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(54) Title: METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

(57) Abstract

This invention relates to a novel series of compounds which are useful in the treatment or prevention of a physiological disorder associated with an excess of stimulation of the human Group I metabotropic glutamate receptors, especially those designated as mGluR5. This invention also provides methods for the treatment of such disorders, as well as pharmaceutical formulations which employ the novel metabotropic glutamate receptor antagonists to which the present invention relates.

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METABOTROPIC GLUTAMATE RECEPTOR ANTAGONISTS

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathway in mammals, and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). See Watkins & Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges, and Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). The excitatory amino acids are of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic." This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA). The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in c-AMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). The metabotropic glutamate receptors can be divided into three subgroups according to their amino acid sequence similarity. Group I includes the receptors designated as mGluR1 and mGluR5; Group II includes mGluR2 and mGluR3; and Group III includes mGluR4, mGluR6, mGluR7, and mGluR8. Pinn and Duvoisin, *Neuropharmacology*, 34(1), 1 (1995). Both the ionotropic and the metabotropic receptor types appear not only to mediate normal synaptic transmission along excitatory pathways, but also participate in the modification of synaptic connections during development and

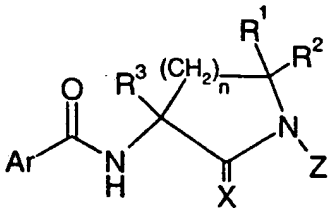
throughout life. Schoepp, Bockaert, and Sladeczek, *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald and Johnson, *Brain Research Reviews*, 15, 41 (1990).

The excessive or inappropriate stimulation of excitatory amino acid receptors leads to neuronal cell damage or loss by way of a mechanism known as excitotoxicity. This process has been suggested to mediate neuronal degeneration in a variety of conditions. The medical consequences of such neuronal degeneration makes the abatement of these degenerative neurological processes an important therapeutic goal.

The metabotropic glutamate receptors are a highly heterogeneous family of glutamate receptors that are linked to multiple second-messenger pathways. These receptors function to modulate the presynaptic release of glutamate, and the postsynaptic sensitivity of the neuronal cell to glutamate excitation. Antagonists of these receptors are useful for the treatment of acute and chronic neurodegenerative conditions, and as antipsychotic, anticonvulsant, analgesic, anxiolytic, antidepressant, and anti-emetic agents. In addition, antagonists of the metabotropic glutamate receptors are useful for the treatment of acute, chronic, persistent, intractable, and neuropathic pain.

The present invention provides antagonists of the Group I human metabotropic glutamate receptors, preferably those designated as mGluR5. The treatment and/or prevention of physiological disorders associated with metabotropic glutamate receptors is hereby furthered.

The present invention encompasses novel compounds of the formula :



Formula I

wherein,

n is 0, 1 or 2;

X is O, S, NH, or NOH;

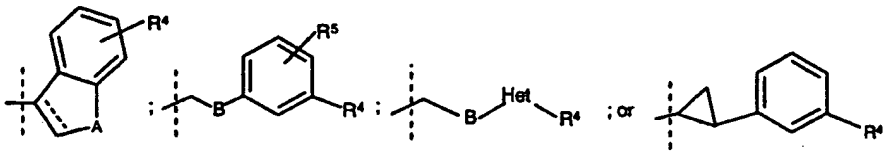
R^1 and R^2 are each independently H, CN, COOR, CONHR, C_1-C_6 alkyl, tetrazole, or R^1 and R^2 together represent "=O";

R is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, -CH_2OH, -CH_2O-alkyl, -COOH;

Ar is an unsubstituted or substituted aromatic or heteroaromatic group;

Z represents a group of the formulae



wherein,

R^4 and R^5 are each independently H, halogen, C_1-C_6 alkoxy , -OAr , C_1-C_6 alkyl, -CF_3, COOR, CONHR, -CN, -OH, COR, -S-(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl)

A is CH_2, O, NH, NR, S, SO, SO_2, CH_2-CH_2, CH_2O, CHOH, C(O); wherein R is as defined above;

B is CHR, CR_2, C_1-C_6 alkyl, C(O), -CHOH, -CH_2-O, -CH=CH, CH_2-C(O), CH_2-S, CH_2-S(O), CH_2-SO_2; -$CHCO_2R$; or –CH-NR_2, wherein R is as defined above

Het is a heterocycle such as furan, thiophene, or pyridine;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention encompasses pharmaceutically acceptable solvates and prodrugs of Formula I in addition to pharmaceutical formulations comprising, as an active ingredient, a compound of Formula I in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

In yet another embodiment, the present invention encompasses a method for the treatment or prevention of a physiological disorder associated with an excess of stimulation of Group I metabotropic glutamate receptors, and preferably those designated as mGluR5, which method comprises administering to a patient in need thereof an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides a method of antagonizing one or more of the actions of L-glutamate at Group I metabotropic glutamate receptors, which method comprises administering an effective amount of a compound of Formula I.

According to yet another aspect, the present invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof as defined hereinabove, for the manufacture of a medicament for antagonizing one or more of the actions of L-glutamate at Group I metabotropic glutamate receptors.

The invention further provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for antagonizing one or more of the actions of L-glutamate at Group I metabotropic glutamate receptors.

The terms and abbreviations used in the present document have their normal meaning in the art, unless otherwise designated.

All temperatures stated herein are in degrees Celsius (°C). All units of measurement employed herein are in weight units except for liquids which are in volume units.

As used herein, the term "C_1-C_6 alkyl" refers to straight or branched, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl.

"Ar" represents an aromatic carbocyclic group consisting of 6-10 atoms in a single ring (i.e. phenyl) or multiple condensed rings (i.e. napthyl), which can be unsubstituted or substituted with 1 or more, preferably 1-5, substituents independently selected from C_1-C_6 alkyl, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, C_1-C_6 alkoxy, carboxy, hydroxy, cyano, halo, trifluoromethyl, nitro, amino, C_1-C_6 acylamino, C_1-C_6 alkylthio, hydroxy (C_1-C_6)alkyl, C_1-C_6 alkyl sulfonyl, halo (C_1-C_6 alkyl).

The term " C_1-C_6 acylamino" represents an acyl group with zero to five carbon, straight, or branched, alkyl chain attached to an amino group.

"Halo" or "halogen" represents chloro, fluoro, bromo or iodo.

"Halo(C_1-C_6)alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms with 1, 2 or 3 halogen atoms attached to it. Typical halo(C_1-C_6)alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibromobutyl, 3-chloroisobutyl, iodo-*t*-butyl, trifluoromethyl and the like.

"Hydroxy(C_1-C_6)alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms with hydroxy group attached to it. Typical

hydroxy(C_1-C_6)alkyl groups include hydroxymethyl, 2-hydroxyethyl, 1-hydroxyisopropyl, 2-hydroxypropyl, 2-hydroxybutyl, 3-hydroxyisobutyl, hydroxy-*t*-butyl and the like.

"C_1-C_6 alkylthio" represents a straight or branched alkyl chain having from one to six carbon atoms attached to a sulfur atom. Typical C_1-C_6 alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio and the like.

The term "C_2-C_6 alkenyl" as used herein represents a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms. Typical C_2-C_6 alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

"C_1-C_6 alkylamino" represents a straight or branched alkylamino chain having from one to six carbon atoms attached to an amino group. Typical C_1-C_6 alkylamino groups include methylamino, ethylamino, propylamino, isopropylamino, butylamino, *sec*-butylamino and the like.

"Di(C_1-C_6 alkyl)amino" represents a straight or branched dialkylamino chain having from one to six carbon atoms attached to an amino group. Typical C_1-C_6 alkyl amino groups include dimethylamino, ethylmethylamino, methylisopropylamino, t-butylisopropylamino, di-t-butylamino, and the like.

The term "heterocycle" or "het" refers to a cyclic group of one or more rings containing one or more hetero atoms, and which can be aromatic or non-aromatic. An "aromatic heterocycle" represents a stable 5 to 7 membered ring containing one to four heteroatoms selected from oxygen, sulfur and nitrogen, and which can be fused with a benzene ring or a 5 to 6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen. A "non-aromatic heterocycle" represents a stable 4 to 7 membered ring containing one or two heteroatoms selected from oxygen, sulphur and nitrogen. Examples of such aromatic and nonaromatic heterocycles include thienyl, thiophenyl, furyl, oxazolyl, isoxazolyl, thiazoyl, isothiazolyl, imidazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, pyrrolyl, piperidinyl, pyridinyl, tetrahydrofuranyl, tetrahydropyranyl, piperazinyl, morpholinyl, thiomorpholinyl, and the like.

"C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *t*-butoxy, pentoxy and the like.

"C_2-C_6 alkanoyl" represents a straight or branched alkyl chain having from one to five carbon atoms attached to a carbonyl moiety. Typical C_2-C_6 alkanoyl groups include ethanoyl, propanoyl, isopropanoyl, butanoyl, *t*-butanoyl, pentanoyl, hexanoyl, 3-methylpentanoyl and the like.

"C_3-C_6 cycloalkyl" represents a saturated hydrocarbon ring structure containing from three to six carbon atoms. Typical C_3-C_6 cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, and the like.

The term "amino-protecting group" or "Prot-" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound. Examples of such amino-protecting groups include "ArCO" wherein "Ar" is defined as above, formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxy-carbonyl ("FMOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups. The species of amino-protecting group employed is usually

not critical so long as the derivatized amino group is stable to the condition of subsequent reactions on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting groups. Preferred amino-protecting groups are "ArCO", trityl, *t*-butoxycarbonyl (*t*-BOC), phthalimido, allyloxycarbonyl and benzyloxycarbonyl. Further examples of groups referred to by the above terms are described by E. Haslam, "Protective Groups in Organic Chemistry", (J.G.W. McOmie, ed., 1973), at Chapter 2; and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis" (1991), at Chapter 7.

The term "carboxy-protecting group" as used in the specification refers to substituents of the carboxy group commonly employed to block or protect the carboxy functionality while reacting other functional groups on the compound. Examples of such carboxy-protecting groups include methyl, ethyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxy-benzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylene-dioxybenzyl, benzhydryl, 4,4'-dimethoxy-benzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, *t*-butyl, *t*-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, *t*-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, 2-(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl and like moieties. Preferred carboxy-protecting groups are allyl, benzyl, ethyl, and *t*-butyl. Further examples of these groups are found in E. Haslam, supra, at Chapter 5, and T.W. Greene, et al., supra, at Chapter 5.

The term "leaving group" as used herein refers to a group of atoms that is displaced from a carbon atom by the attack of a nucleophile in a nucleophilic substitution reaction. The term "leaving group" as used in this document encompasses, but is not limited to, activating groups.

The term "activating group" as used herein refers a leaving group which, when taken with the carbonyl (-C=O) group to which it is attached, is more likely to take part in an acylation reaction than would be the case if the group were not present, as in the free acid. Such activating groups are well-known to those skilled in the art and may be, for example, succinimidoxy, phthalimidoxy, benzotriazolyloxy, benzenesulfonyloxy, methanesulfonyloxy, toluenesulfonyloxy, azido, or -O-CO-(C_4-C_7 alkyl).

The term "solid support" refers to a solid and insoluble substrate, within a combinatorial chemistry reaction medium, capable of containing chemical functionality.

The term "solid supported scavenger" refers to a solid and insoluble substance, within a combinatorial chemistry reaction medium, containing chemical functionality which is reactive with impurities sought to be removed from the reaction medium.

The term "scaffold reactant" refers to the reactant within a combinatorial chemistry reaction medium which contains the invariant or core region of the library of compounds synthesized by the combinatorial process.

The compounds encompassed by the present invention can have multiple asymmetric centers. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to one of two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers. The term "rel" refers to the relative stereochemistry of a given compound and is used in nomenclature when there is more thatn one asymmetric center in a structure. As used herein, "rel-(R,R)" denotes a racemic mixture of (R,R)- and (S,S)- isomers and "rel-(R,S)" denotes a racemic mixture of (R,S)- and (S,R)- isomers.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing

the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = ((E^1 - E^2)/(E^1 + E^2)) \text{ X } 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981. Examples of resolutions include recrystallization techniques or chiral chromatography.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (*sinister*) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

In addition to the (R)-(S) system, the older D-L system is also used in this document to denote absolute configuration, especially with reference to amino acids. In

this system a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix "D" is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

As noted supra, this invention includes prodrugs and pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "prodrug" as used herein refers to metabolically labile esters of the compounds of Formula I.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts. In addition, it is understood in the art that such salts may exist as hydrates.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, g-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically

acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

The preferred compounds of the present invention are those represented by Formula I wherein,

a) n is 0 or 1;
b) X is O or S;
c) R^1 and R^2 are each independently H, or R^1 and R^2 together represent "=O";
d) R^3 is C_1-C_6 alkyl;
e) Ar is meta-substituted aryl (aromatic , heteroaromatic)
f) R^4 is H, F, Cl, or OMe;
g) A is $-CH_2-$, -O-, or $-(CH_2)_2-$; and
h) B is C_1-C_3 alkyl, methylene, methylmethylene, $-CH_2O-$, -CH=CH-, -CHOH.

More preferred are the compounds represented by Formula I wherein,

a) n is 1
b) X is S;
c) R^3 is methyl;
d) Ar is 3-bromophenyl, 3-chlorophenyl, 6-chloropyridin-2-yl, or 5-chlorofuran-2-yl;

e) Z is 1-indanyl, 3-chlorophenethyl, or 3-fluorophenethyl;

f) A is $-CH_2-$; and

g) B is methylene.

Especially preferred compounds of the present invention are those specifically exemplified herein as Example 1, Example 2, Example 25, Example 26, Example 29, and Example 30.(See infra.) Most preferred are the compounds of Example 25 and Example 30.

This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formula I. Many of these compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

This invention also encompasses methods for the treatment or prevention of a physiological disorder associated with an excess of stimulation of Group I metabotropic glutamate receptors, preferably the receptor designated as mGluR5, which method comprises administering to a patient in need thereof, an effective amount of a compound of Formula I.

The term "patient" as used herein refers to a mammal such as a mouse, guinea pig, rat, dog, or human. It is understood that the preferred patient is a human. The term "treatment" (or "treating" or "treat") as used herein includes its generally accepted meaning which encompasses prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or a resultant symptom. As such, the methods of the present invention encompass both therapeutic and prophylactic uses. The term "effective amount" as used herein refers to the amount or dose of the compound of Formula I which provides the desired effect in the patient under diagnosis or treatment.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose of compound administered, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disorder involved; the degree of or involvement or the severity

of the disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

The term "neurodegenerative condition or disease" refers to neurological disorders including, for example, cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, perinatal hypoxia, cardiac arrest, hypoglyemic neuronal damage, ocular damage and retinopathy, and idiopathic and drug-induced Parkinson's Disease. The compounds of the present invention are also useful for the treatment of pain. "Pain" as used herein refers to acute, chronic, persistent, intractable, and neuropathic pain.

A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of a compound used in the present methods of treatment. Preferably, the daily dose will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

The methods of the present invention are carried out by administering a Group I metabotropic glutamate receptor antagonist at a dose which provides an effective level of compound in the body. The metabotropic glutamate receptor antagonist may be administered in a single dosage form, or may be administered in combination with other therapies. Oral administration is a preferred route of administration. However, oral administration is not the only route or even the only preferred route. The compound may be administered by other routes including the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the compounds and the convenience of the patient and the caregiver.

The compounds of the present invention may be administered as a pharmaceutical compositions, and so pharmaceutical compositions incorporating the compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such compositions contain an effective amount of a compound of the present invention, which effective amount is

related to the daily dose of the compound to be administered. Each dosage unit may contain the daily dose of a compounds, or may contain a fraction of the daily dose, such as one-half or one-third of the dose. Alternatively, each dosage unit may contain the entire dose of the compounds. The amount of a compound to be contained in each dosage unit depends on the identity of the compound chosen for the therapy, and other factors such as the indication for which the treatment is being given.

Preferred compounds for use in the methods of the present invention are those represented by Formula I wherein,

a) n is 0 or 1;

b) X is O or S;

c) R^1 and R^2 are each independently H, or R^1 and R^2 together represent "=O";

d) R^3 is C_1-C_6 alkyl;

e) Ar is meta-substituted aryl (aromatic , heteroaromatic)

f) R^4 is H, F, Cl, or OMe;

g) A is $-CH_2-$, -O-, or $-(CH_2)_2-$; and

h) B is C_1-C_3 alkyl, methylene, methylmethylene, $-CH_2O-$, -CH=CH-, -CHOH.

More preferred for use in the methods of the present invention are those compounds represented by Formula I wherein,

a) n is 1;

b) X is S;

c) R^3 is methyl;

d) Ar is 3-bromophenyl, 3-chlorophenyl, 6-chloropyridin-2-yl, or 5-chlorofuran-2-yl;

e) Z is 1-indanyl, 3-chlorophenethyl, or 3-fluorophenethyl;

f) A is $-CH_2-$; and

g) B is methylene.

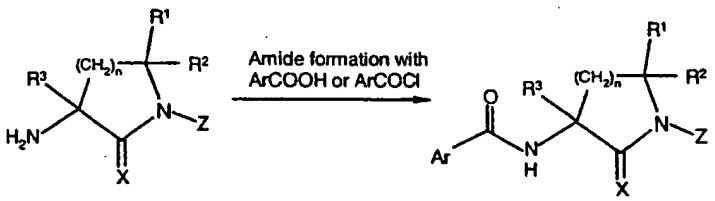
Especially preferred compounds for use in the methods of the present invention are those specifically exemplified herein as Example 1, Example 2, Example 25, Example 26, Example 29, and Example 30.(See infra.) Most preferred for use in the present methods are the compounds of Example 25 and Example 30.

The compounds of the present invention can be synthesized by a variety of procedures well known to those of ordinary skill in the art. For example, U.S. Patent No. 4,666,901, herein incorporated by reference, describes solution phase synthesis of monocyclic lactams useful as angiotensin converting enzyme(ACE) inhibitors. As with any compound, the particular order of steps required to produce a specific compound given by Formula I is dependent upon the particular compound being synthesized, the starting material, and the relative lability of the substituents as appreciated by one of ordinary skill in the art.

General procedures, useful for synthesizing the compounds of the present invention are depicted by the following schemes. Substituents appearing in these descriptions are as defined above, unless otherwise indicated. Note, these are descriptions of general methods and as such, are in no way to be interpreted as limiting the scope of the present invention. All reagents and starting materials are readily available to the ordinarily skilled artisan.

Scheme I

General method from amine or amine salt



Formula II Formula I

Compounds of Formula I are prepared under standard conditions from primary amines (Formula II), or an amine salt of (II), such as for example a hydrochloride salt, by amide formation with a carboxylic acid derivative. Many methods are convenient

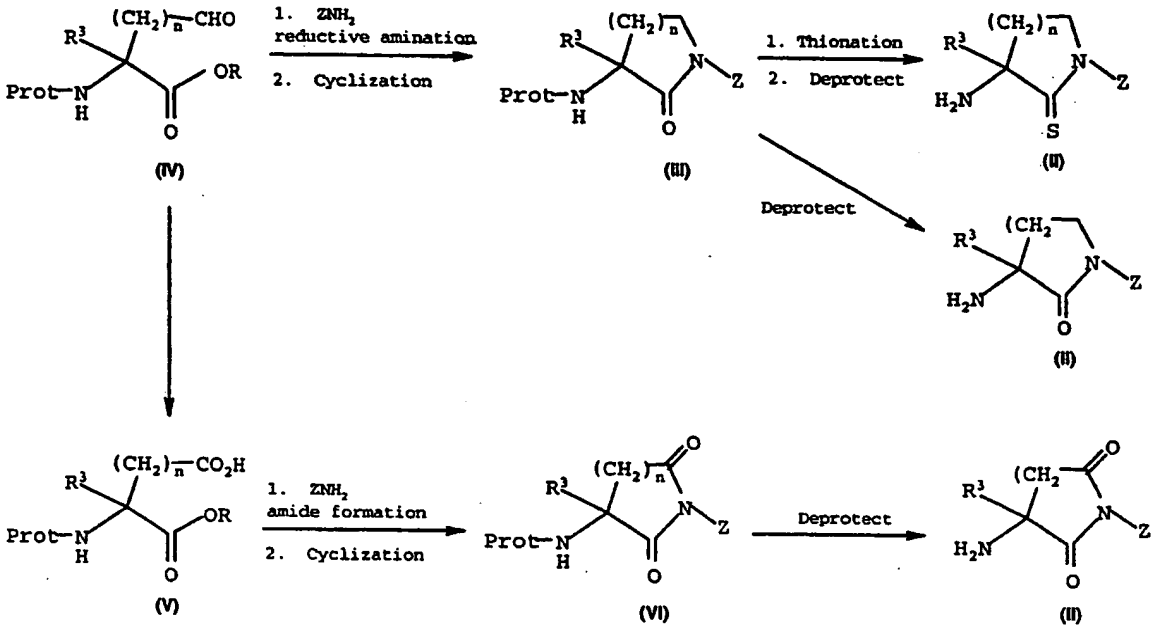
for amide formation, including: (a) reaction with an acid chloride, ArCOCl, in the presence of a base such as triethylamine or pyridine, in an inert solvent such as dichloromethane, chloroform, or tetrahydrofuran, preferably at a temperature between 0 and 40 °C; (b) activation of a carboxylic acid with 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) in the presence of a base such as triethylamine or pyridine, in an inert solvent such as dichloromethane, chloroform, or tetrahydrofuran, preferably at a temperature between 0 and 40 °C; (c) activation of a carboxylic acid with EDC (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) and PP-HOBT (piperidino-piperidine derivative of 1-hydroxy benzotriazole useful as a catlyst for amide formation as described in US Patent Application 09/213734, the entire contents of which is herein incorporated by reference) in a mixture of solvents such as dichloromethane and dimethylformamide, preferably at room temperature between 20 and 30 °C, followed by filtration removal, on an SCX column, of basic reagents from the neutral amide product of Formula I; (d) activation of a carboxylic acid to form a mixed anhydride with, for example, acetic anhydride or trifluoroacetic anhydride, in the presence of a dehydrating agent; and (e) activation of a carboxylic acid with, for example, N, N'-carbonyldiimidazole (CDI) or N, N'-dicyclohexylcarbodiimide (DCC).

Compounds of Formula I, in which X is S, are prepared by thionation of compounds of Formula I in which X is O, by reaction with, for example, 4-methoxyphenylthionophosphine sulphide dimer (Lawesson's reagent) or phosphorus pentasulphide, in an inert solvent such as toluene, preferably at a temperature between 20 and 110 °C.

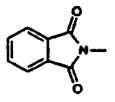
Compounds of Formula I, and the intermediates leading to them, can be present in isomeric forms. These isomers can be separated by standard methods such as column chromatography for diastereoisomers, or preparative chiral HPLC for enantiomers.

Scheme II

Preparation of amine (or amine salt)



Amines (Formula II) or their salts, as part of the present invention, are prepared from an intermediate aldehyde (Formula IV). The aldehyde (IV) contains a protected amine, in which the protecting groups (Prot-) include t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), ArCO, or phthalimido where Prot -NH is



and also contain an ester group, COOR, where R represents C_1-C_6 alkyl, such as, for example, methyl. Boc is the preferred protecting group. Note, where the aldehyde (IV) has the protecting group ArCO , such as, for example, 3-bromobenzoyl, then reductive amination with Z-NH2 and cyclization produces the compounds of Formula I directly.

The amines (Formula II), or their salts, are prepared by at least one of the following methods. Note, the particular method chosen is dependant upon the desired structure of the amine (Formula II) sought.

Amines (Formula II) in which X is O

Reductive amination of the aldehyde (IV) with a primary amine ZNH_2 is conducted in the presence of reducing agents such as sodium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride, in alcoholic solvents such as

methanol or in solvents such as tetrahydrofuran or acetic acid. Preferably, this step is performed at a temperature between 0 and 80 °C. Cyclization to the lactam (Formula III) can occur spontaneously at room temperature (depending on ring size and Z-group), or can be induced by heating in solvents such as toluene or methanol/triethylamine, preferably at a temperature between 60 and 110 °C, or can be effected by reagents such as trimethylaluminium in inert solvents such as toluene, preferably at a temperature between 20 and 80 °C.

The lactam (Formula III) is deprotected using standard methods known in the art, with the exact method chosen being dependant on the particular protecting group employed. Where Prot is Boc, the lactam (Formula III) is treated with an acid, such as HCl, in the presence of a solvent such as, for example, dioxan or diethylether, preferably at a temperature between 0 and 40 °C, to produce the amine salt. Alternatively, the lactam can be treated with an acid, such as trifluoroacetic acid, preferably at a temperature between 0-40 °C, to produce the amine salt. When Prot is Cbz, the lactam (Formula III) is hydrogenolyzed with hydrogen in the presence of 5% palladium on carbon, in solvents such as methanol, ethanol, toluene, or acetic acid at room temperature, in order to produce the amine. Where Prot is phthalimido, the lactam (Formula III) is deprotected by reagents such as hydrazine in solvents, such as ethanol, preferably at a temperature between 20 and 80 °C to produce the amine (II).

Amines (II) in which X is S

Lactams (Formula III) are thionated by reaction with, for example, 4-methoxyphenylthionophosphine sulphide dimer (Lawesson's reagent) or phosphorus pentasulphide, in an inert solvent such as toluene, preferably at a temperature between 20 and 110 °C. Deprotection is then carried out using standard methods as described above, with the exact method chosen being dependant on the particular protecting group employed.

Amines (II) in which R1 and R2 together are "=O"

Conversion of the aldehyde (Formula IV) to the acid (Formula V) can be carried out using oxidizing agents such as ruthenium tetroxide (formed from sodium periodate and catalytic ruthenium trichloride), in sovents such as a mixture of chloroform, acetonitrile, and water, preferably at a temperature between 0° and 60° C. To form the amide, the acid (Formula V) is reacted with ZNH_2 using standard methods such as

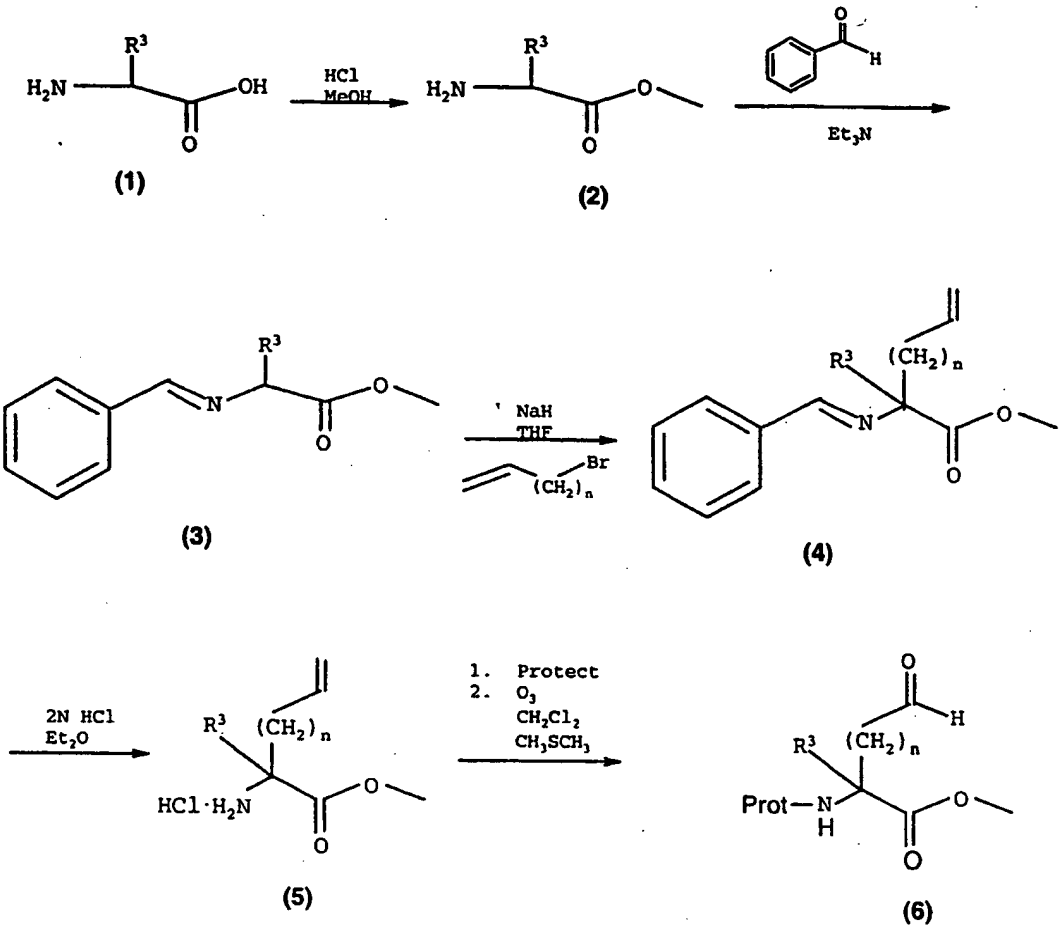
activation of the acid with 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) in the presence of a base such as triethylamine or pyridine, in an inert solvent such as dichloromethane, chloroform or tetrahydrofuran, preferably at a temperature between 0 and 40 °C. Cyclization of the amide to form Formula IV is carried out by treatment with an alkali metal base, such as sodium hydride or lithium bis(trimethylsilyl)amide, in an inert solvent such as dimethylformamide or tetrahydrofuran, preferably at a temperature between 0 and 80 °C.

Deprotection is then carried out using standard methods as described above, with the exact method chosen being dependent on the particular protecting group employed.

Aldehyde starting reactants, Formula IV in Scheme II above, may be synthesized by typical methods, well known to those of ordinary skill in the art. As such, the following procedure, which describes one such method useful for generating the aldehyde reactant (Formula IV) employed in the synthesis of compounds of Formula I, should not be interpreted as limiting the present invention in any way. The skilled artisan will recognize that other methods are available for the synthesis of aldehydes, and that the particular method chosen will be dependent on the final product sought.

Scheme III

Preparation of aldehyde starting reactant



(1) (2) (3) (4) (5) (6)

Preparation of (2)

To an amino acid, methanol is added followed by HCl (bubbled) until the solid dissolves. The reaction is heated to reflux and left to stand at room temperature overnight. When the reaction is 90% complete, additional HCl gas is bubbled followed by further reflux. After standing at room temperature for 2 days the methanol is evaporated to yield a white solid which is triturated with diethyl ether. The solid is collected by filtration and dried under vacuum to afford the intermediate (2).

Preparation of (3)

(2) is added to a flask, followed by a solution of freshly distilled benzaldehyde in a solvent such as dichloromethane. A solution of triethylamine in dichloromethane is then added, followed by additional dichloromethane to facilitate stirring. After stirring overnight at room temperature, the solvents are removed by evaporation and the solid residue is triturated with diethyl ether. The solid (e.g. Et_3N-HCl) is removed by filtration and the filtrate is evaporated to afford the intermediate (3).

Preparation of (4)

To a flask equipped with a mechanical stirrer and a nitrogen inlet, sodium hydride is added as a dispersion in an oil, such as mineral oil. The sodium hydride is slurried with hexane to remove the mineral oil then a solution of intermediate (3) in, for example, tetrahydrofuran, is then added dropwise with continuous stirring for approximately 30 minutes. After addition of (3) a solution of allyl bromide or 4-bromo-1-butene in a solvent, such as tetrahydrofuran, is added dropwise until a precipitate forms. After additional stirring, the reaction is allowed to stand overnight at room temperature. Water is then added to the mixture and the reaction extracted with diethyl ether three times. Intermediate (4) is obtained after drying the combined extracts over sodium sulfate, filtering, and evaporating the filtrate.

Preparation of (5)

A solution of intermediate (4) in diethyl ether is stirred vigorously with HCl for approximately 3 hours. The layers are separated and the aqueous layer extracted with diethyl ether. The ether layers are discarded and sodium chloride is added to the aqueous solution which is then basified to a pH ~ 9.5 with, for example, sodium hydroxide, then extracted with dichloromethane. The dichloromethane layers are combined, dried (with for example Na_2SO_4), filtered, and evaporated to yield the free base of intermediate (5) as a colorless oil. HCl gas is then bubbled into this solution, followed by evaporation and addition of ethyl acetate. The crystals formed (intermediate 5), can then be collected by filtration.

Preparation of (6)

The amino group of intermediate (5) is protected, for example with ArCO, then dissolved in a solvent such as dichloromethane. The reaction is cooled under a stream of nitrogen then treated with a stream of ozone until the reaction turns blue.

Methyl sulfide is added to the reaction after which the reaction is allowed to stand at room temperature overnight. The reaction is extracted with saturated $NaHCO_3$ and saturated NaCl, then dried over Na_2SO_4, filtered, and evaporated to yield the aldehyde of intermediate (6). Alternatively, the protected intermediate (5) is treated with sodium periodate and osmium tetroxide in a solvent such as dioxan and H_2O.

In order to preferentially prepare one optical isomer over its enantiomer, the skilled practitioner can proceed by one of two routes. The practitioner may first prepare the mixture of enantiomers and then separate the two enantiomers. A commonly employed method for the resolution of the racemic mixture (or mixture of enantiomers) into the individual enantiomers is to first convert the enantiomers to diastereomers by way of forming a salt with an optically active salt or base. These diastereomers can then be separated using differential solubility, fractional crystallization, chromatography, or like methods. Further details regarding resolution of enantiomeric mixtures can be found in J. Jacques, et al., "Enantiomers, Racemates, and Resolutions" (1991).

In addition to the schemes described above, the practitioner of this invention may also choose an enantiospecific protocol for the preparation of the compounds of Formula I. Such protocols usually produce compounds in which greater than 95 percent of the title product is the desired enantiomer.

In addition to the conventional synthesis methods described above, the compounds of the Formula I wherein X is O can also be generated using the methods of combinatorial chemistry. The techniques of combinatorial chemistry are employed to generate large numbers (i.e. 10^2 to 10^6) of compounds which are therein referred to as "libraries". Theoretically, the total number of compounds that may be produced for a given library is limited only by the number of reagents available to form the substituents on the variable regions of the library's general formula. Further, combinatorial processes lend themselves to automation, both in the generation of compounds and in their screening for biological activity.

Combinatorial chemistry can be used both to generate highly "diverse" compound libraries as well as to optimize a particular lead compound from a previous round of syntheses through generation of "directed libraries". As used herein, "diverse library" refers to a library where the substituents on the combinatorial library scaffold of the compounds are highly vaiable in terms of their constituent atoms and/or molecular

weight, and the library, therefore, is no a collection of closely related homologues or analogues. "Directed library", as used herein, refers to a collection of compounds created for the purpose of optimizing a lead compound, wherein each compound shares at least one common substituent on the library scaffold, while maintaining variability at another substituent, thus allowing optimization of the variable moeity.

Combinatorial chemistry may be performed in a manner wherein libraries of compounds are generated as mixtures, with complete isolation of the individual compounds postponed until after a positive finding of biological activity. However, a preferred form of combinatorial chemistry is "parallel array synthesis" wherein individual compounds are synthesized contemporaneously, but are retained in separate reaction vessels. For example, library compounds may be held in the individual wells of a 96-well microtiter plate (Beckman Corp., Fullerton CA.). Use of microtiter plates, or an equivalent apparatus, is of particular advantage because of its adaptability to automated robotic machinery.

As appreciated by those of ordinary skill in the art, conventional combinatorial chemistry can be performed on a "solid support" or a polymer. As used herein polymer refers to a molecule composed of resin monomers to which the compounds of the present invention are attached. Suitable polymer resins for use in the present invention must be inert to the reaction conditions for compound synthesis. Suitable polymers include Merrifield type resins, Wang type resins, and polyamide type resins. Examples of these include polystyrene(Bachem Inc.), polyamide resins, POLYHIPE™ resin (Aminotech Co., Canada), p-alkoxybenzyl alcohol resin, polystyrene resin grafted with polyethylene glycol, or polydimethylacrylamide resin. (See generally: *Solid Phase Peptide Synthesis*, J.M. Sheppard et al., 2nd Ed, 1984, Pierce Chemical Co., Illinois). Preferably, polystyrene is used in the process of the present invention.

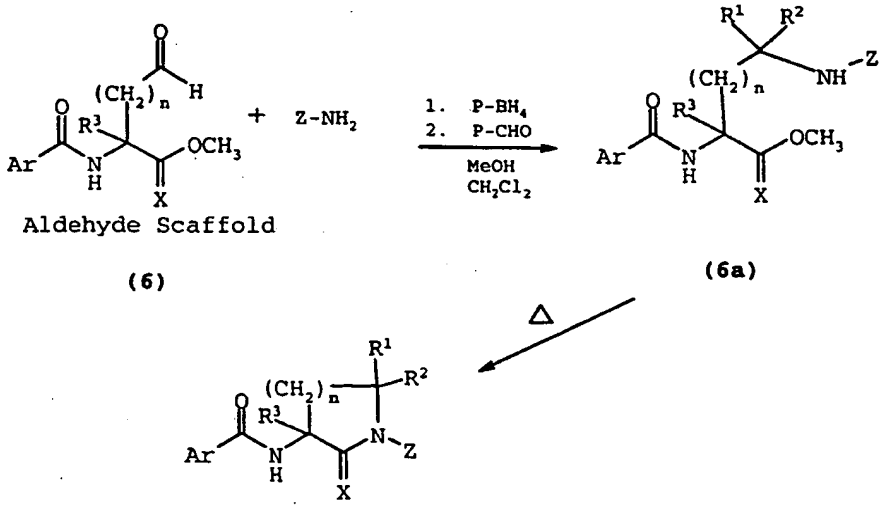
Here, the library "scaffold reactant" is tethered to the sold support via a chemical linker. Reactants are added to the reaction vessel to modify the scaffold reactant, followed by cleavage of the final product from the solid support. In this solid phase synthesis, variations in the reactants added to the scaffold produce the desired structural diversity of the library's general formula. Separation of the product and the unreacted reactants is accomplished by filtration, decantation, or washing, all techniques well appreciated by those of ordinary skill in the art.

Alternatively, solution phase combinatorial processes can also be used to generate the compounds of the present invention. Here, an excess of a particular reaction reagent may be added to a soluble solution of a scaffold reactant, driving the solution phase reaction to completion. In this process, unreacted soluble reagents may then be removed from the reaction medium using a "solid supported scavenger".

A library of lactam compounds, comprising the Group I metabotropic glutamate receptor antagonists of the present invention, may be generated combinatorially by reacting an aldehyde scaffold reactant with a primary amine reactant. The following scheme (Scheme IV), represents a general process for a conventional solution phase combinatorial synthesis of the compounds given by Formula I, wherein X is O, R^1 and R^2 are H, and further as defined above.

Scheme IV

Conventional Solution Phase Combinatorial synthesis



The aldehyde scaffold reactants are synthesized essentially as described in Scheme III above, where the scaffold reactant is represented by intermediate (6). The scaffold reactants ((n) equivalents) are each placed in a reaction vessel, followed by an excess (1.1(n) equivalents) of a soluble primary amine, Z-NH_2, wherein Z is as defined

previously. This reaction is maintained at a suitable temperature and for a suitable time to permit reaction between the various aldehyde scaffold reactants and the various primary amine reactants. Next, is added a large excess (~ 4.0(n) equivalents) of a solid supported reducing agent, represented by P-BH_4 in Scheme IV, wherein P represents a solid support (i.e polymer) and BH_4 is the reducing agent borohydride. Those of ordinary skill in the art will appreciate that other solid supported reducing agents such as cyanoborohydride or triacetoxyborohydride can replace boroydride in Scheme IV and, therefore, the depiction of borohydride as the reducing agent in Scheme IV should not be interpreted as limiting the invention. The reaction is maintained at a suitable temperature and for a suitable time to allow reaction of intermediates to yield secondary amines.

The unreacted primary amine is removed from the reaction by addition of a solid supported aldehyde scavenger, represented by P-CHO in Scheme IV above. The reaction is maintained at a suitable temperature and for a suitable time to permit reaction of said excess primary amine with said scavenger. The separation of the solid supported reducing agent and scavenger from the reaction vessel is done by any of a number of available chemical or physical methods well known to those of ordinary skill in the art. Such physical methods, applicable to all members of a diverse library include: (i) filtration; (ii)centrifugation; (iii) decantation; (iv) washing, and the like. Filtration is particularly useful and is practiced by passing the reaction medium of each library compound through a filter apparatus which retains the excess solid supported reactants while allowing the solution containing the desired compound to pass into a separate vessel.

Finally, the solution phase is placed in a glass vial and capped for approximately 12 hours at 60°C. This heating, in turn, promotes cyclization of intermediate II in Scheme IV above, to yield the final lactam product as represented by Formula I.

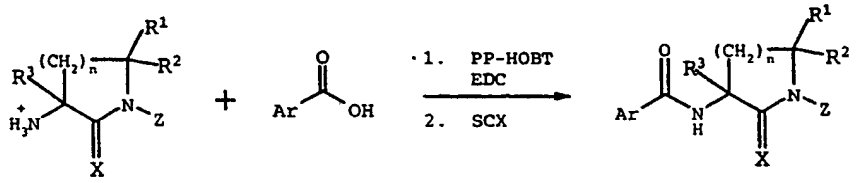
Combinatorial chemistry can also be employed to optimize a particular substituent on a lead compound generated from a previous round of synthesis. As used herein, a "lead compound" refers to a lactam compound, synthesised using the methods of the present invention, which has been shown to possess the desired biological activity of a human Group I metabotropic glutamate receptor antagonist. When employed for lead optimization, combinatorial chemistry results in a "directed library", wherein each

compound within the library shares at least one common functional substituent, while maintaining variability at the remaining substituent sites on the library scaffold. The "directed library" is, thus, in its entirety, a collection of closely related homologues or analogues. For example, combinatorial chemistry can be employed to generate a directed library of lactam compounds of Formula I, wherein each compound within the library shares a common lactam amine functionality substituent, while maintaining variability at the amide functional substituent, thus allowing optimization of the amide moiety of the lead compounds of Formula I.

The following scheme, Scheme V, depicts a combinatorial process useful for the optimization of the amide substituent of the combinatorial scaffold of Formula I, wherein X is O. In this process, an amine reactant is placed in each of an array of reaction vessels, followed by the addition of various carboxylic acid derivatives. The library of lactam products, made from this combinatorial process, share a common amine functionality substituent, while maintaining variability at the amide moiety.

Scheme V

Optimization of amide moiety



Compounds of Formula I are prepared from primary amines (Formula II), or an amine salt of (II), such as for example a hydrochloride salt, by amide formation with a carboxylic acid derivative. Many methods are convenient for amide formation, including: (a) reaction with an acid chloride, ArCOCl, in the presence of a base such as triethylamine or pyridine, in an inert solvent such as dichloromethane, chloroform, or tetrahydrofuran, preferably at a temperature between 0 and 40 °C; (b) activation of a carboxylic acid with 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent) in the presence of a base such as triethylamine or pyridine, in an inert solvent such as dichloromethane, chloroform, or tetrahydrofuran, preferably at a temperature between 0 and 40 °C; (c) activation of a carboxylic acid with EDC (1-(3-Dimethylaminopropyl)-3-

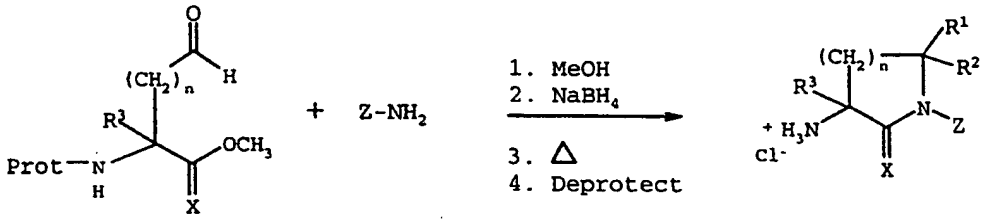
ethylcarbodiimide hydrochloride) and PP-HOBT (piperidino-piperidine derivative of 1-hydroxy benzotriazole useful as a catlyst for amide formation as described in US Patent Application 09/213734, the entire contents of which is herein incorporated by reference) in a mixture of solvents such as dichloromethane and dimethylformamide, preferably at room temperature between 20 and 30 °C, followed by filtration removal, on an SCX column, of basic reagents from the neutral amide product of Formula I; (d) activation of a carboxylic acid to form a mixed anhydride with, for example, acetic anhydride or trifluoroacetic anhydride, in the presence of a dehydrating agent; and (e) activation of a carboxylic acid with, for example, N, N'-carbonyldiimidazole (CDI) or N, N'-dicyclohexylcarbodiimide (DCC).

Compounds of Formula I, and the intermediates leading to them, can be present in isomeric forms. These isomers can be separated by standard methods such as column chromatography for diastereoisomers, or preparative chiral HPLC for enantiomers.

The starting amine salt employed in Scheme V is generated by reductive amination in the usual manner, followed by cyclization, according to the following scheme(Scheme VI).

Scheme VI

Reductive amination of protected aldehyde followed by cyclization



Formula II

Reductive amination of a protected aldehyde scaffold reactant (IV) with a primary amine ZNH_2 is conducted in the presence of reducing agents such as sodium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride, in alcoholic solvents such as methanol or in solvents such as tetrahydrofuran or acetic acid.

Preferably, this step is performed at a temperature between 0 and 80 °C. Cyclization to the lactam can occur spontaneously at room temperature (depending on ring size and Z-group), or can be induced by heating in solvents such as toluene or methanol/triethylamine, preferably at a temperature between 60 and 110 °C, or can be effected by reagents such as triethylaluminium in inert solvents such as toluene, preferably at a temperature between 20 and 80 °C.

The lactam is deprotected using standard methods known in the art, with the exact method chosen being dependant on the particular protecting group employed. The skilled artisan will recognize that other protecting groups can be employed in Scheme VI, other than Boc and, thus, the depiction of Boc, in Scheme VI should not be construed as limiting the present invention in any way. Where Boc is employed, the lactam is treated with acid in the presence of a solvent such as, for example, dioxan or diethylether, preferably at a temperature between 0 and 40 °C, to produce the amine salt (II). The amine salt is then converted to the free base by well known methods. Preferably, the amine salt used is the hydrochloride salt. Alternatively, the lactam can be treated trifluoroacetic acid, preferably at a temperature between 0-40 C, to produce the amine salt (II). When Prot is Cbz, the lactam is hydrogenolyzed with hydrogen in the presence of 5% palladium on carbon, in solvents such as methanol, ethanol, toluene, or acetic acid at room temperature, in order to produce the amine (II). Where Prot is phthalimido, the lactam is deprotected by reagents such as hydrazine in solvents, such as ehtanol, preferably at a temperature between 20 and 80 °C to produce the amine (II).

The biological activity of the compounds of the present invention was evaluated by employing a phosphoinositide hydrolysis assay or a calcium mobilization assay. As mentioned supra, "metabotropic" glutamate receptors are G-protein, or secondary messenger-linked, receptors. As such, these receptors are linked to multiple second messenger systems which enhance phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in c-AMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). A general description of the phosphoinositide hydrolysis assay employed in the present invention is given as follows:

(a) Cell cultures:

mGluR5 or mGluR1 receptor expressing cell lines are cultured in DMEM supplemented with 5% heat inactivated fetal calf serum, sodium pyruvate (1mM), glutamine (1mM), penicillin (100U/ml), streptomycin (100mg/ml), HEPES (10mM), geneticin G418 (0.5mg/ml) and hygromycin B (0.2mg/ml). Confluent cultures are passaged weekly.

(b) Phosphoinositide Hydrolysis Assay:

Transfected cells are seeded into 24 well culture plates at 2.5 x 10^5 cells per well in medium containing no added glutamine and cultured at 37°C in a humidified atmosphere of 5% CO_2 in air. After 24hr, the cells are labeled with [^{3}H]-inositol (4uCi/ml) for a further 20hr. Cells are washed in assay medium containing HEPES (10mM), inositol (10mM) and lithium chloride (10mM). Antagonists are added to the cell cultures 20 min prior to the addition of quisqualate and then the culture is further incubated in the presence of agonist for 60 min. The reaction is terminated by replacing the medium with acetone:methanol (1:1) and then incubating the cultures on ice for 20 min. Separation of the [^{3}H]-inositol phosphates is carried out by Sep -Pak Accell Plus QMA ion exchange chromatography (Waters, Millipore Ltd., UK) according to the method described by Maslanski and Busa (*Methods in Inositide Research*; ed. Irvine, R.F. pp. 113-126; New York, Raven Press Ltd. 1990). The [^{3}H]-inositol monophosphate (INS P1) fraction is eluted with 0.1M triethyl ammonium bicarbonate buffer and radioactivity measured by liquid scintillation counting. Following the measurement of radioactivity for each fraction eluted, IC_{50} calculations were made for each antagonist examined. Representative compounds of the present invention generated IC_{50} values equal to or less than 30μM in the phosphoinositide assay herein described, when mGluR5 expressing cell lines were employed.

Alternatively, the biological activity of the compounds of the present invention can be determined employing an assay which monitors intracellular calcium ion concentration in response to metabotropic glutamate receptor activation. As stated supra, activation of G-protein coupled receptors triggers a sequence of events which contribute to alterations in intracellular calcium concentration. By monitoring alterations in calcium ion concentration in response to metabotropic glutamate receptor activation, one can identify compounds functional as metabotropic glutamate receptor antagonists. A general

description of a calcium flux assay which can be employed to determine the biological activity of the compounds of the present invention is given as follows:

(a) Plate Preparation:

Plates containing cells expressing mGluR5 or mGluR1 are prepared using standard methods well known to those of skill in the art. Reagent plates are prepared containing 160µl/well of buffer (1% DMSO or compound in 1%DMSO buffer) and additional plates are prepared containing 260µl/well of 10µM Glutamate in assay buffer.

(b) Calcium Flux Assay:

Media is removed from the plates containing the cells expressing mGluR5 using a hand held aspirator or standard plate washer. 50µl of 10µM Fluo3 Dye is added to each well which in turn will emit fluorescence upon binding to calcium ions. Cells are incubated at room temperature for approximately 90 minutes to allow the Fluo3 Dye to load into the cells. The dye is then aspirated and replaced with 50ul of buffer. The plates are placed in a fluorescent light imaging plate reader (FLIPR) such that the plate containing the buffer or compound is to the right of the cell plate, while the plate containing the glutamate is placed to the left of the cell plate. The FLIPR is programmed to take background fluorescence readings for 10 seconds then add buffer or compound to the cell plates. After 3 minutes, the FLIPR adds 100µl of 10µM glutamate to mobilize cellular calcium ion stores and fluorescence is measured for about a minute. Fluorescence values for cells containing buffer are compared relative to cells containing mGluR5 antagonist compound. Percent inhibition of mGluR5 elicited calcium ion influx, as indexed by fluorescence, is calculated for each compound. Representative compounds of the present invention at a concentration of 30µM produce percent inhibition values equal to or higher than 70 % in the calcium flux assay described herein, when mGluR5 expressing cells are employed .

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical formulation comprising a compound of formula I and a pharmaceutically-acceptable carrier, diluent, or excipient. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the

compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium sterate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. Compositions of the inventions may be formulated so as to provide quick, sustained, or delayed released of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

Quantity

	(mg/capsule)
Compound of Formula I	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Compound of FormulaI	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight %
Compound of Formula I	0.25
Ethanol	29.75
Propellant 22 (chlorodifluoromethane)	70.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets each containing 60 mg of active ingredient are made as follows:

Compound of Formula I	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules each containing 80 mg medicament are made as follows:

Compound of Formula I	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories each containing 225 mg of active ingredient may be made as follows:

Compound of Formula I	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

Compound of Formula I	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

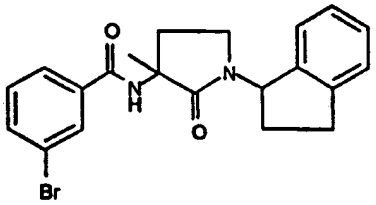
An intravenous formulation may be prepared as follows:

Compound of Formula I	100 mg
Mannitol	100 mg
Purified water to total	5 ml

The following Examples further illustrate the compounds of the present invention and the methods of their synthesis. The examples are not intended to be limiting to the scope of the invention in any respect, and should not be so construed. The abbreviations employed in the following examples are commonly used in the field and would be readily understood by a practitioner in the field. For example; "Ph" refers to a phenyl group; "Me" refers to a methyl group; "Et" refers to an ethyl group; "Bu" refers to a butyl group; "t-Bu" refers to a tert-butyl group; "Mp. °C" refers to the melting point of a compound if it is a solid or, in the alternative, notes the form of the compound at ambient temperature; "MS" defines the mass of the particular compound as determined using mass spectroscopy; "MW" defines the molecular weight of the particular compound; "eq" refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "min" refers to minutes; "h" refers to hours; "°C" refers to degrees Celsius; "NMR" refers to nuclear magnetic resonance spectroscopy; "IR" refers to infrared spectroscopy; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ"refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "aq" refers to aqueous; "TFA" refers to trifluoroacetic acid: "iPrOAc"

refers to isopropyl acetate; "iPr" refers to an isopropyl group; "EtOAc" refers to ethyl acetate; and "RT" refers to room temperature.

Example 1



rel-(R,R)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-one.

Mp. °C: Oil

MW: 412.9

i) A solution of triethylamine (37.2ml) in dichloromethane (50ml) was added to a stirred solution of methyl L-alanine hydrochloride (37.3g) and benzaldehyde (27.2ml) in dichloromethane (350ml) cooled in an ice bath under nitrogen atmosphere. After stirring overnight the thick suspension was evaporated and the residue triturated with diethylether (200ml). The solid was filtered, washed with ether and the filtrate washed with water, then brine solution. The ether solution was dried over magnesium sulphate, filtered and evaporated to give a yellow liquid. Distillation gave the imine as a colourless liquid.

ii) The preceding imine (36.5g) in dry tetrahydrofuran (20ml) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil, 7.64g) in tetrahydrofuran (200ml) at room temperature under nitrogen atmosphere. After 20 min and approximately one quarter of the addition the reaction became exothermic. After 1h the clear red solution was cooled in an ice bath and allyl bromide (19.4ml) was added dropwise. After stirring overnight the

yellow suspension was diluted with diethylether (100ml) and cautiously quenched with water (100ml). The mixture was extracted twice with ether and the combined ether solutions washed with water (3x), then brine solution. The ether solution was dried over magnesium sulphate, filtered and evaporated to give an orange oil of the α-allyl imine.

iii) A mixture of the α-allyl imine (91.7g) in diethylether (450ml) and 2M hydrochloric acid (450ml) was stirred rapidly for 4h at room temperature. The aqueous solution was separated, washed with ether and then basified to pH 11 with sodium hydroxide solution. The aqueous solution was saturated with sodium chloride and extracted twice with dichloromethane. The dichloromethane extracts were dried over magnesium sulphate, filtered and evaporated to give a yellow oil of methyl α-allylalanine.

iv) 3-bromobenzoyl chloride (35.5ml) was added dropwise to a stirred solution of methyl α-allylalanine (30g) and triethylamine (37.3ml) in dichloromethane (330ml) at room temperature under nitrogen. After 4h, the dichloromethane solution was successively washed with 2M hydrochloric acid, saturated aqueous bicarbonate (2x) and brine solution. The dichloromethane solution was dried over magnesium sulphate, filtered and evaporated. The residual oil was purified by chromatography through a pad of silica eluting with ethyl acetate:hexane 80:20 to give methyl N-(3-bromobenzoyl)allylalanine.

v) Method 1

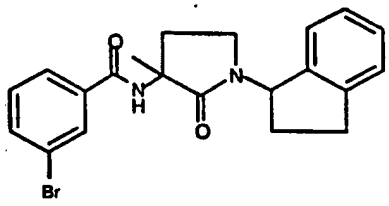
A solution of sodium periodate (37.5g) in water (250ml) was added dropwise over 15 min to a stirred solution of methyl N-(3-bromobenzoyl)-α-allylalanine (34.2g) and several crystals of osmium tetroxide (approx. 30mg) in dioxan (390ml) and water (50ml). After 5h at room temperature, water was added and the mixture extracted with diethylether (3x). The ether extracts were washed with water and saturated aqueous sodium bicarbonate, then was dried over magnesium sulphate, filtered and evaporated. The residual oil was purified by chromatography through a pad of silica eluting with 2% methanol in dichloromethane to give methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine as a viscous oil.

Method 2

A solution of methyl N-(3-bromobenzoyl)-α-allylalanine (38.9g) in dichloromethane (250ml) was cooled to -78°C and ozone bubbled through until a blue colour persisted (3½h). The excess ozone was purged by bubbling oxygen through the solution until the colour changed back to yellow. Dimethylsulphide (200ml) was added and the solution allowed to stand at room temperature overnight. The dichloromethane solution was washed with saturated sodium bicarbonate solution (3x), brine, and then was dried over magnesium sulphate, filtered and evaporated. The residual oil was purified by chromatography through a pad of silica eluting with 2% methanol in dichloromethane to give methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine as an oil.

vi) 1-amino indane was reacted with methyl N-(3-bromobenzoyl)-α-(2-oxoethyl) alanine as described in Example 2 to give the title product.

Example 2



(R,R)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-one.

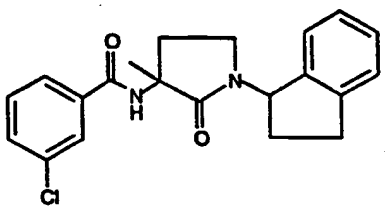
Mp. °C: white glass

MS: [M+H] 413, 415

R-(-)-1-aminoindane (8.12g) was added to a stirred solution of N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (20g) in methanol (400ml) at room temperature under nitrogen. After 1h solid sodium borohydride (4.6g) was added portionwise over 20 min causing effervescence and a temperature rise to 32°C. After 1½h water was added and the mixture extracted with diethylether (2x). The ether extracts were washed with brine (3x), dried over magnesium sulphate, filtered and evaporated to a pale viscous oil. The oil was dissolved in methanol (416ml) and triethylamine (41.6ml) and heated under reflux for 24h. The solution was evaporated and the residue dissolved in ethyl acetate, washed with 2M hydrochloric acid (2x), brine(3x), dried over magnesium sulphate, filtered and evaporated to a white foam. The mixture was purified by flash

chromatography eluting with ethyl acetate:hexane 80:20 to give isomer-1 followed by isomer- 2, the title product as a white solid. Impure column fractions were chromatographed again to give a further crop of the title product.

Example 3



3-[(3-Chlorobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-one.

Mp. °C: 160-161

MS: [M+H] 369, 371

i) Di-t-butyldicarbonate (57.0g) was added to a stirred solution of methyl α-allylalanine (37.4g) in 10% triethylamine/ methanol (160ml) under nitrogen. The mixture was heated to 45°C for 1h, then allowed to stand overnight at room temperature. The solution was evaporated to give methyl N-(t-butoxycarbonyl)-α-allylalanine as a yellow oil.

ii) A solution of methyl N-(t-butoxycarbonyl)-α-allylalanine (29.3g) in dichloromethane (120ml) was cooled to -78°C and ozone bubbled through until a blue colour persisted (4½h). The excess ozone was purged by bubbling oxygen through the solution until the colour changed back to yellow.

Dimethylsulphide (80ml) was added and the solution allowed to stand at room temperature overnight. The dichloromethane solution was washed with saturated sodium bicarbonate solution (3x), brine (2x), dried over magnesium sulphate, filtered and evaporated to give methyl N-(t-butoxycarbonyl)-α-(2-oxoethyl)alanine as an oil.

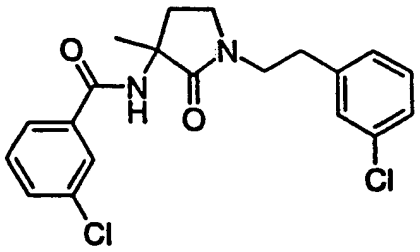
iii) A solution of methyl N-(t-butoxycarbonyl)-α-(2-oxoethyl)alanine (5g) and 1-aminoindane (2.85g) in methanol (50ml) was stirred at room temperature under nitrogen atmosphere for 1.25h. The reaction mixture was then cooled to 0°C and sodium borohydride (1.54g) added portionwise, After addition, the reaction mixture was stirred at room temperature for 1h, concentrated in vacuo, diluted with water and extracted twice with diethylether. The combined extracts was washed with water and brine, dried over magnesium sulphate, filtered and evaporated to give methyl 2-(t-butoxycarbonyl)amino-4-(indanyl-1-amino)-2-methylbutanoate as a brown oil.

iv) A solution of methyl 2-(t-butoxycarbonyl)amino-4-(indanyl-1-amino)-2-methylbutanoate (6.7g) in toluene (100ml) was heated at reflux under a nitrogen atmosphere for 24h. After cooling the solvent was evaporated to give a red oil. The crude oil was purified on flash silica eluting with diethylether:hexane 3:2 to give the diastereomeric mixture of 3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-one as an oil.

v) A stirred solution of 3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-one (5.1g) in dioxan (20ml) was treated with a 4M solution of hydrogen chloride in dioxan (20ml). After 3h at room temperature, the solution was evaporated to a foam. The mixture was dissolved in dichloromethane and washed with a saturated solution of sodium bicarbonate. The organic phase was dried over magnesium sulphate, filtered and evaporated to give 3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-one as a red oil.

vi) To a stirred solution of 3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-one (0.51g) and dried triethylamine (0.34ml) in dichloromethane (20ml) was added a solution of 3-chlorobenzoyl chloride (0.42g) in dichloromethane (10ml). After stirring overnight at room temperature, the reaction mixture was washed with 2M hydrochloric acid, water and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated to an oil. The diastereomers were separated on flash silica eluting with diethylether to give the title compound in the slower eluting fraction as a white solid, m.p. 160-161°C.

Example 4



3-[(3-Chlorobenzoyl)amino]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one.

Mp. °C: 137-138

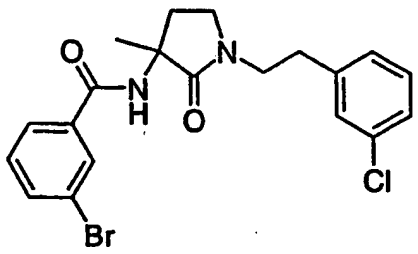
MS: [M+H] 391, 393, 395

i) The reaction between methyl N-(t-butoxycarbonyl)-α-(2-oxoethyl)alanine (4.04g) and 3-chlorophenethylamine (2.81g) in methanol (40ml) was carried out as in example 3(iii). After reduction with sodium borohydride (1.08g) and aqueous work-up, the crude product was crystallised from cyclohexane to give 3- (t-butoxycarbonyl)amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one as a white solid.

ii) Following the procedure described in example 3(v), 3-(t-butoxycarbonyl)amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one was converted to 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one to give a brown oil.

iii) Following the procedure described in example 3(vi), 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one was treated with 3-chlorobenzoyl chloride in the presence of triethylamine. After work-up and crystallisation of the crude from methanol, the title compound was obtained as a white solid, m.p. 137-138°C.

Example 5



3-[(3-Bromobenzoyl)amino]-1-(3-chlorophenethyl)-3-methylpyrrolidine-2-one.

MS: 434.9, 436.9

i.) Reductive amination of a protected aldehyde was performed in the usual fashion. Approximately 0.61g of a t-Boc protected aldehyde, as given in Scheme VI above, was weighed out into a 100ml round bottom flask (reaction vessel). Approximately 0.67g (1.1 (n) equivalents) of 2-(3-chlorophenyl) ethylamine was transferred to the reaction vessel by dilution with MeOH and rinsing with MeOH. Total volume was approximately 6.0ml. The reaction vessel was shaken on a platform shaker for 2 hours to permit mixing of the reactants. The reactions were then evaporated, followed by addition of MeOH to the original volume. After the reaction cooled in an ice/ethanol bath, approximately 185 mg (5mmol) of the reducing agent sodium borohydride was added while mixing with a boiling stick. Reactions were allowed to mix gently on a platform shaker for 2 days at room temperature to allow cyclization of the lactam product. (crude weight ~ 880mg.) Mass spectroscopy revealed cyclized lactam product without amine intermediates. Chromatography of the lactam product was performed over 62g. silica, applied in $CHCl_3$ to a column equilibrated with 60:40 EtOAc:Hexane, and eluted with 100ml of 60:40 EtOAc:Hexane, 100 ml 70:30 EtOAc:Hexane, and 100 ml 80:20 EtOAc:Hexane. The weight of chromatographed product was ~ 439mg. for a percent yield of approximately 50%.

ii) The t-Boc protecting group was removed form the product of step (i) by dissolving the lactam in 2N HCl in dioxane in a round bottom flask. After one hour the reaction was evaporated and the resulting amine•HCl was obtained.

Directed combinatorial synthesis, essentially as described in **Scheme V** above, was performed on the lactam product obtained from part (i) in order to optimize the amide functional substituent of Formula I. The amine•HCl was dissolved in THF to make a 0.05M solution and 0.7ml (35umoles) of the amine•HCl was aliquoted into each of a 9 X 11 array of 4ml reaction vials. To each vial, next was added 0.6ml (30umol) of a .05M carboxylic acid solution (for this example 3-bromobenzoic acid) dissolved in 25% DMF in $CHCl_3$, 0.2ml (35 umol) of PP-HOBT, and 0.4ml (40umol) of 0.1M EDC•HCl solution in DCM. The reaction vials were then capped and rocked for 16 hours at room temperature.

The reaction was then purified over 500 mg. varian SCX columns conditioned with 2.5ml MeOH and 2.5ml 10% MeOH:$CHCl_3$. The reaction mixture was loaded as is and washed with 2.5ml 10% MeOH:$CHCl_3$ and eluted by gravity. The products were evaporated with high nitrogen flow at 25° hot plate setting. 0.2ml of $CHCl_3$ and re-evaporated then 0.2ml of $CHCl_3$ was added and the product was evaporated again at 45°C. Yield of product was ~100% and NMR showed less than 1 equivalent of DMF after MeOH evaporation. Finally, the product was dissolved in 2.5ml of 1:1 MeOH:$CHCl_3$ and mass spectroscopy and TLC were performed. Title product was then transferred to a 96 well plate for biological activity determination.

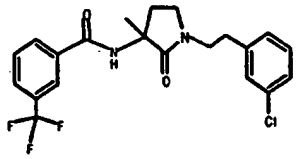
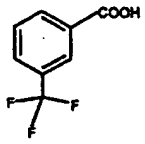
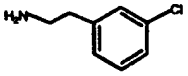
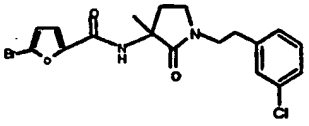
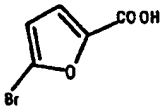
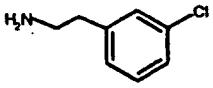
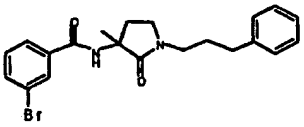
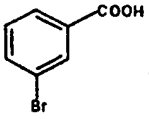
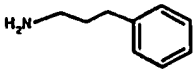
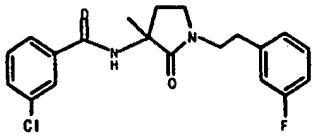
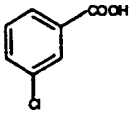
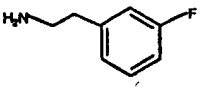
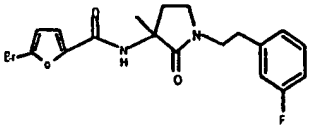
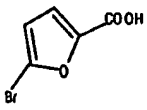
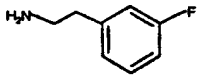
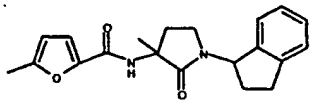
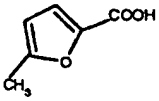
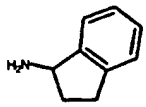
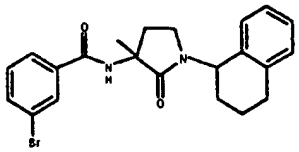
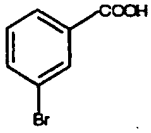
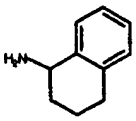
Examples 6 – 12

The following table (Table I) illustrates additional compounds (Examples 6 –12), produced using the directed combinatorial methods, essentially as described for Example 5 above. The abbreviations used in the table are commmonly used in the field and would be readily appreciated by a practitioner in the field.

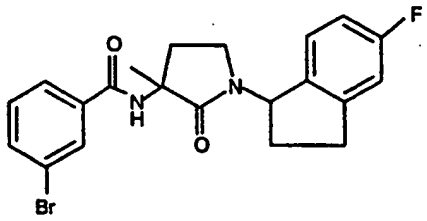
In the Table I below, the first column gives the example number for the compound. The second column provides the structure of the exemplified compound. The next two columns describe the substitutions of the particular example compound. "ArCOOH" provides the carboxylic acid (or derivative) employed to optimize the amide functionality of the lactam product essentially as described in **Scheme V** above, wherein

"Ar" is as defined previously. "Z-NH_2" provides the primary amine employed in the reductive amination of the protected aldehyde scaffold reactant as described in **Scheme VI**, wherein "Z" is as described previously. The next column, entitled "Stereo" describes the stereochemistry profile of the exemplified compound. "MW", defines the molecular weight of the compound and "MS" defines the mass of the compound as as determined by mass spectroscopy.

Table I

Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS
6						425.00
7						424.9 426.9
8						417.00
9						375.00
10						408.9 410.9
11				enantiomer pair 2		339.10
12				enantiomer pair 2		427.0 429.0

Example 13



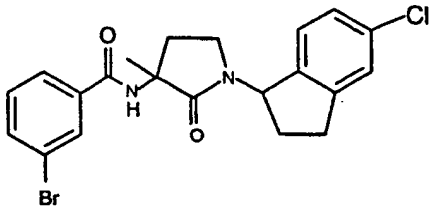
3-[(3-Bromobenzoyl)amino]-1-(5-fluoroindan-1-yl)-3-methylpyrrolidin-2-one.

Mp. °C:180-181

MS: [M+H] 431, 432, 433, 434

The reaction between methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (0.66g) and 1-amino-5-fluoroindane (0.30g) in methanol (10ml) was carried out as described in example 3(iii). Reduction with sodium borohydride (0.15g) and aqueous work-up gave an orange oil. The crude oil was heated at reflux in methanol (10ml) in the presence of triethylamine (1.3ml) for 16h. After cooling the solvent was evaporated and the residue partitioned between diethylether and 2M hydrochloric acid. The aqueous phase was washed with diethylether and the combined organic phases washed with water and brine, dried over magnesium sulphate, filtered and evaporated to a white foam. Separation of the diastereomers on flash silica eluting with ethyl acetate:hexane 70:30 gave the desired diastereomer in the slower eluting fraction. The resulting oil was crystallised from ethyl acetate to give the title compound as a white solid, m.p. 180-181°C.

Example 14



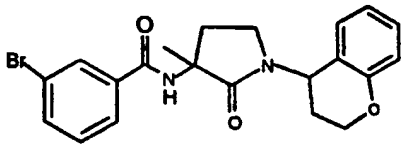
3-[(3-Bromobenzoyl)amino]-1-(5-chloroindan-1-yl)-3-methylpyrrolidin-2-one.

Mp. °C: 211-214

MS: [M+H] 447, 449, 451

The reaction between methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (0.66g) and 1-amino-5-chloroindane (0.34g), was followed by reduction with sodium borohydride and carried out as described in example 13. The crude oil was heated at reflux in methanol (10ml) in the presence of triethylamine (1.3ml) for 16h. After similar work-up and chromatography the title compound was obtained as a white solid, m.p. 211-214°C.

Example 15



3-[(3-Bromobenzoyl)amino]-1-(2,3-dihydro-4H-benzopyran-4-yl)-3-methylpyrrolidin-2-one.

Mp. °C: 172-173

MS: [M+H] 429, 431

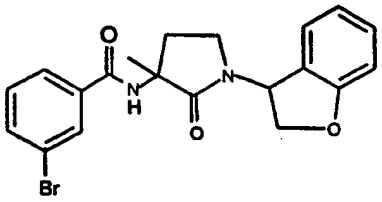
i.) A stirred suspension of 4-chromanone (25g), potassium carbonate (23.3g) and hydroxylamine hydrochloride (11.6g) in ethanol (200ml) was heated under reflux for 1½h. After cooling, water (125ml) was added to crystallise the oxime product.

ii.) A solution of the oxime (5.0g) in acetic acid (50ml) and Adams catalyst (0.25g) was hydrogenated at 50 psi for 1h. The catalyst was filtered and the filtrate evaporated to a colourless oil. The oil was suspended in 2M aqueous sodium hydroxide solution (50ml) and extracted with dichloromethane (2x, 50ml). The extracts were dried, filtered and evaporated to a colourless oil. Distillation using a bulb to bulb apparatus gave 2,3-dihydro-4H-benzopyran-4-amine, b.p.100-120°C @ 0.1mbar.

iii.) A solution of 2,3-dihydro-4H-benzopyran-4-amine (0.3g) and methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (0.65g) in methanol (13ml) was stirred at room temperature under nitrogen. After 1h solid sodium borohydride (0.15g) was added portionwise. The mixture effervesced and became warm. After 1h water (20ml) was added and the mixture extracted with diethylether (2x, 20ml). The extracts were washed with brine solution (20ml), dried, filtered and evaporated to a viscous oil (0.78g). A solution of

the oil in methanol (13ml) and triethylamine (1.3ml) was heated under reflux for 24h. The mixture was evaporated and the residue dissolved in ethyl acetate (20ml) and washed with 2M hydrochloric acid (2x, 20ml) and brine (20ml). The ethyl acetate solution was dried, filtered and evaporated to a white foam (0.61g) containing a mixture of the two diastereomers of the title compound. Chromatography on flash silica eluting with ethyl acetate:hexane 80:20 gave isomer-1 followed by the title compound, isomer-2. m.p. 172-173°C.

Example 16



3-[(3-Bromobenzoyl)amino]-1-(2,3-dihydrobenzofuran-3-yl)-3-methylpyrrolidin-2-one.

Mp. °C: 173

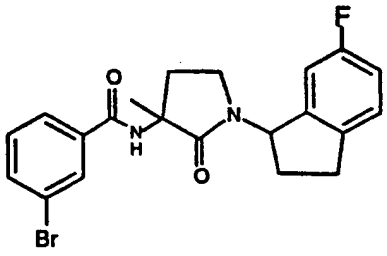
MS: [M+H] 415, 417

i) A stirred mixture of 3-coumaranone(25g), sodium acetate (30.6g) and hydroxylamine hydrochloride (25.7g) in ethanol (125ml) was heated under reflux for 1h. After cooling water (150ml) was added to crystallise the oxime product as yellow needles.

ii) Freshly prepared aluminium amalgam (from 10g foil) was added to a stirred mixture of the oxime (4.47g) in ethanol (60ml) under nitrogen. The exothermic reaction caused the temperature to rise to reflux after 10min. Additional ethanol (150ml) was added and the reaction was kept at reflux for 4h. The grey voluminous inorganic solid was filtered and the filtrate evaporated. The residue was dissolved in diethylether and washed with 2M aqueous sodium hydroxide solution (50ml). The ether solution was dried, filtered and evaporated and the liquid residue distilled to give 3-amino-2,3-dihydrobenzofuran. b.p. 160-170°C @ 4mbar.

iii) The reaction between 3-amino-2,3-dihydrobenzofuran (0.15g) and methyl N-(t-bromobenzoyl)-α-(2-oxoethyl)alanine (0.65g) was carried out as described in example 15(iii) and the diastereomeric mixture separated on flash silica to give the slower eluting title compound, isomer-2. m. p. 173°C.

Example 17



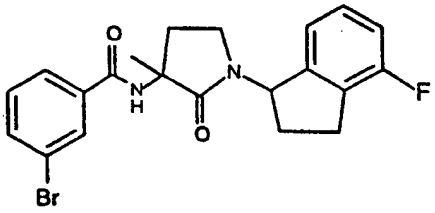
3-[(3-Bromobenzoyl)amino]-1-(6-fluoroindan-1-yl)-3-methylpyrrolidin-2-one.

Mp. °C: 196-197

MS: [M+H] 431, 433

The reaction between methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (0.70g) and 1-amino-6-fluoroindane (0.34g), was followed by reduction with sodium borohydride and was carried out as described in example 13. After work-up and chromatography eluting with ethyl acetate:hexane 1:1 and then 70:30, the title compound was obtained as a white solid, m.p. 196-197°C.

Example 18



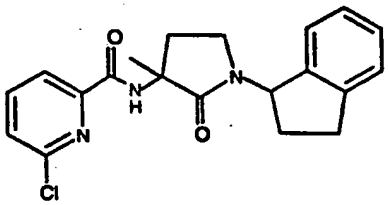
3-[(3-Bromobenzoyl)amino]-1-(4-fluoroindan-1-yl)-3-methylpyrrolidin-2-one.

Mp. °C: 193-194

MS: [M+H] 431, 433

The reaction between methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (0.76g) and 1-amino-4-fluoroindane (0.37g), was followed by reduction with sodium borohydride and was carried out as described in example 13. After work-up and chromatography the title compound was obtained as a white crystals from ethyl acetate:hexane, m.p. 193-194°C.

Example 19



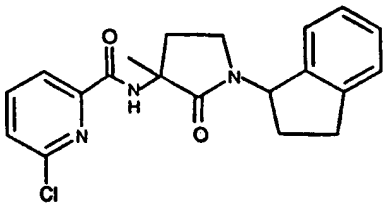
rel-(R,S)-3-[(6-Chloropyridin-2-yl)carboxamido]-1-(1-indanyl)-3-methylpyrrolidin-2-one.

Mp. °C: 130-132

MS: [M+H] 370, 372

The reaction between 3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-one (0.33g) and 6-chloro-2-pyridinecarbonyl chloride (0.28g) was carried out as described in example 3(vi). After non acidic aqueous work-up the crude product was partially separated into the respective diastereomers on flash silica eluting with dichloromethane:ethyl acetate 5:1. The faster eluting diasteroisomer was crystallised from ethyl acetate-hexane to give the title compound as a white solid, m.p. 130-132°C.

Example 20



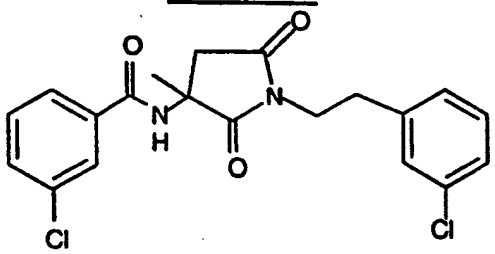
rel-(R, R)-3-[(6-Chloropyridin-2-yl)carboxamido]-1-(1-indanyl)-3-methylpyrrolidin-2-one.

Mp. °C: 148-151

MS: [M+H] 370, 372

The slower eluting fraction from the chromatography described in example 19 gave the second diasteroisomer as an oil which after trituration with diethylether gave the title compound as a white solid, m.p. 148-151°C

Example 21



3-[(3-Chlorobenzoyl)amino]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2,5-dione.

Mp. °C: 135-136

MS: [M+H] 405, 407, 409

i) To a stirred solution of methyl N-(t-butoxycarbonyl)-α-(2-oxoethyl)alanine (15.0g) in a mixture of chloroform:acetonitrile:water (1:1:1.5, 56ml) cooled in an ice bath was added sodium periodate (38.1g) and ruthenium (III) chloride hydrate (0.66g). The mixture was kept at room temperature for 3½h, then quenched with isopropanol (150ml), filtered through a pad of celite and evaporated. The oil was dissolved in toluene and evaporated to remove traces of isopropanol leaving methyl N-(t-butoxycarbonyl)-α-(carboxymethyl)alanine as a brown oil.

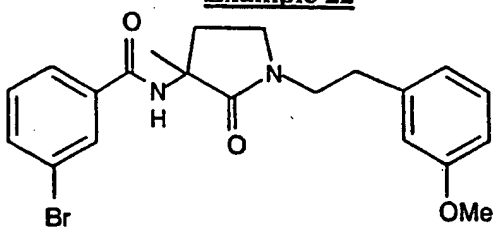
ii) A mixture of methyl N-(t-butoxycarbonyl)-α-(carboxymethyl)alanine (3.0g), 2-chloro-1-methylpyridinium iodide (2.94g) and dried triethylamine (3.2ml) in dichloromethane (30ml) was stirred at room temperature for 1h. A solution of 3-chlorophenethylamine (1.79g) in dichloromethane (5ml) was then added. The reaction mixture was stirred at room temperature for 1½h, then washed with 2M hydrochloric acid, water, a saturated solution of bicarbonate and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated to a brown oil. The crude product was purified on flash silica eluting with ethyl acetate:hexane 1:1 to give methyl 2-(t-butoxycarbonyl)amino-3-(3-chlorophenethyl)carbamoyl-2-methylpropanoate as an oil.

iii) To a stirred solution of methyl 2-(t-butoxycarbonyl)amino-3-(3-chlorophenethyl)carbamoyl-2-methylpropanoate (1.7g) in dried tetrahydrofuran (100ml) under nitrogen atmosphere, was added a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1M, 4.69ml). After 4h at room temperature, the reaction mixture was quenched with water (100ml) and acidified with 2M hydrochloric acid. A yellow solid was filtered and dried in vacuo at 60°C to give 3-(t-butoxycarbonyl)amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2,5-dione.

iv) A stirred solution of 3-(t-butoxycarbonyl)amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2,5-dione (0.42g) in dioxan (10ml) was treated with a solution of hydrogen chloride in dioxan (4M, 10ml) and stirred at room temperature for 24h. The reaction solution was evaporated to a solid, dissolved in water and washed with diethylether. The aqueous phase was made basic with aqueous saturated bicarbonate and extracted twice with dichloromethane. The combined extracts were dried over magnesium sulphate, filtered and evaporated to give 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2,5-dione as a white solid.

v) Following the procedure described in example 3(vi), 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2,5-dione (0.37g) was treated with 3-chlorobenzoyl chloride (0.26g) in the presence of triethylamine (0.21ml). After 1½h, the reaction was worked up as described to give a yellow oil, then purified on flash silica eluting with ethyl acetate:hexane 1:1, to give the title compound as a white solid, m.p. 135-136°C.

Example 22



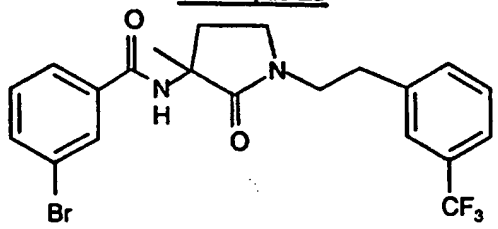
3-[(3-Bromobenzoyl)amino]-1-(3-methoxyphenethyl)-3-methylpyrrolidin-2-one.

Mp. °C: viscous glass

MS: [M+H] 431, 433

The reaction between 3-methoxyphenethylamine (0.15g) and methyl N-(3-bromobenzoyl)(2-oxoethyl)alanine (0.33g) was carried out as described in example 15(iii) followed by purification on flash silica eluting with ethyl acetate:hexane 75:25 to give the title compound as a colourless viscous glass.

Example 23



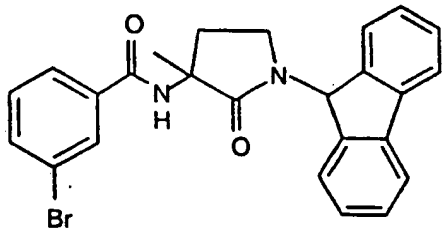
3-[(3-Bromobenzoyl)amino]-1-methyl-3-trifluoromethylphenethylpyrrolidin-2-one.

Mp. °C: viscous glass

MS: [M+H] 469, 471

The reaction between 3-trifluoromethylphenethyl amine (0.19g) and methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (0.33g) was carried out as described in example 15(iii) followed by purification on flash silica eluting with ethyl acetate:hexane 75:25 to give the title compound as a colourless viscous glass.

Example 24



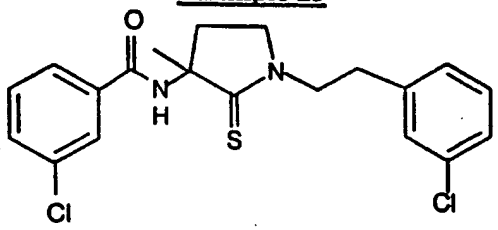
3-[(3-Bromobenzoyl)amino]-1-(9-fluorenyl)-3-methyl-pyrrolidin-2-one

Mp. °C: 217-218

MS: [M+H] 461, 463

The reaction between 9-aminofluorene hydrochloride (0.22g) and methyl N-(t-butoxycarbonyl)-α-(2-oxoethyl)alanine (0.33g) was carried out as described in example 15(iii) with additional heating in toluene for three days. The crude product was recrystallised from toluene (6ml) to give the title compound as a white solid, m.p. 217-218°C.

Example 25



3-[(3-Chlorobenzoyl)amino]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione.

Mp. °C: 77-78

MS: [M+H] 407, 409, 411

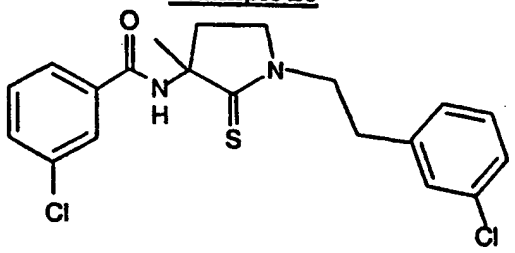
i) To a stirred solution of 3-(t-butoxycarbonyl)amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one (14.5g) in toluene (100ml) was added 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (9.12g) and the mixture heated to reflux for 2h. The mixture was cooled and evaporated to a red oil and partially purified on silica eluting with ethyl acetate:hexane (1:6) to give 3-(t-butoxycarbonyl)amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione as an orange oil contaminated with reagent by-product.

ii) The deprotection of 3-(t-butoxycarbonyl)amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione (5.0g) was carried out as described in example 21(iv) allowing 6h for the completion of the reaction, to give 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione as a brown oil.

iii) Following the procedure described in example 3(vi), 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione (0.25g) was treated with 3-chlorobenzoyl chloride (0.16g) in the presence of triethylamine (0.25ml). After 1h, the reaction was worked up as described and

the resulting oil was purified on silica eluting with ethyl acetate:hexane (1:2, then 2:3) to give the title compound as a white solid, m.p. 77-78°C.

Example 26



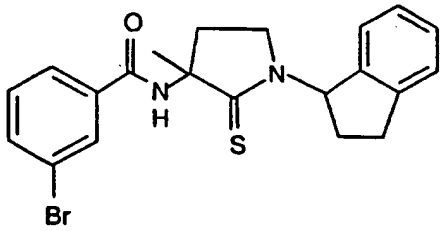
(S)-3-[(3-Chlorobenzoyl)amino]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione.

Mp. °C: Oil

MS: [M+H] 407, 409, 411

The title compound was separated from the racemate in example 25 by preparative chiral HPLC on a 250x4.6mm. id. CHIRALCEL-OD column at a temperature of 40°C eluting at 11.0min with hexane:isopropanol (9:1) at 1ml/min to give an oil.

Example 27



rel-(R,R)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-thione.

Mp. °C: 127-128

MS: [M+H] 429, 431

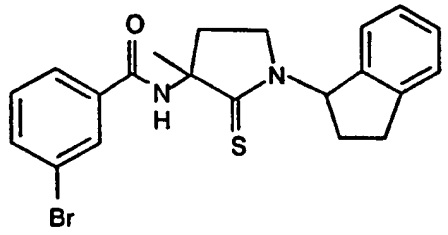
i) Following the procedure described in example 25(i) 3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-one (2.0g) was treated with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide(2.55g) in toluene (10ml). After 4h the solvent was

evaporated and the crude oil purified on flash silica eluting with ethyl acetate:hexane (1:1) to give 3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione as a white solid.

ii) The deprotection of 3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione (0.9g) was carried out as described in example 3(v) to give 3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione as solid.

iii) Following the procedure described in example 3(vi) 3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione(0.3g) was treated with 3-bromobenzoyl chloride (0.29g) in the presence of triethylamine (0.18ml). The resulting diastereomeric mixture was partially separated on flash silica eluting with diethylether:hexane (1:1), the slower eluting fractions were combined and evaporated to give the title compound as a white solid, m.p. 127-128°C.

Example 28



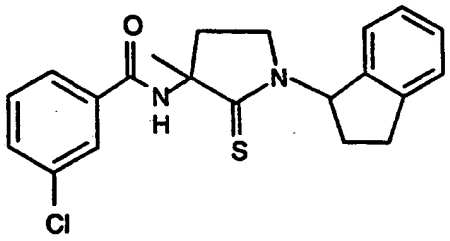
rel-(R,S)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-thione.

Mp. °C: 60-61

MS: [M+H] 429, 431

The faster eluting fractions from the chromatography described in example 27(iii) gave the title compound as a white solid, m.p. 60-61°C.

Example 29



(S,R)-3-[(3-Chlorobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-thione.

Mp. °C: viscous glass

MS: [M+H] 385, 387

i) A solution of R-(-)-1-aminoindane (8.4g) and methyl N-(t-butoxycarbonyl)-α-(2-oxoethyl)alanine (14.7g) in methanol (150ml) was stirred at room temperature for 1h under nitrogen. Solid sodium borohydride (4.54g) was added portionwise over a period of 30min cooling to 20-25°C. After 1h the solution was evaporated to a small volume and water was added. The mixture was extracted with ethyl acetate (2x, 100ml) and the extracts washed with brine (2x, 50ml). The organic phase was dried over magnesium sulphate, filtered and evaporated to a yellow viscous oil. A solution of the oil in toluene (100ml) was heated under reflux for 20h, then evaporated to a brown oil. The crude mixture of diastereomers was purified on flash silica eluting with ethyl acetate:hexane 45:55 to give isomer-1 (S,R)-3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-one followed by isomer-2, (R,R)-3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-one.

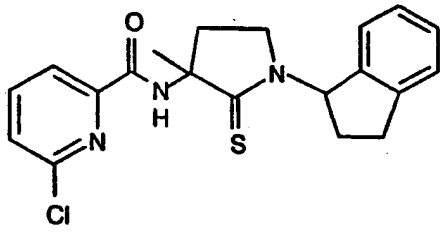
ii) A solution of (S,R)-3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-one (4.4g) in toluene (50ml) was heated to distill approximately 10ml of toluene to ensure an anhydrous solution. After cooling, 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (2.83g) was added and the mixture heated to reflux for 1h. The mixture was evaporated and the residue purified on silica eluting with dichloromethane to give (S,R)-3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione as a pale yellow solid.

iii) A solution of 4M hydrogen chloride in dioxan (20ml) was added to (S,R)-3-(t-butoxycarbonyl)amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione (2.7g). The solid dissolved and after 2h at room temperature the solution was evaporated to dryness. The

residual solid was triturated with diethylether (30ml) and the white solid of (S,R)-3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione hydrochloride filtered, m.p. 213 °C.

iv) A solution of 3-chlorobenzoyl chloride (0.15g) in dichloromethane (1ml) was added to a stirred solution of (S,R)-3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione hydrochloride (0.20g) and triethylamine (0.17g) in dry dichloromethane (2ml) at room temperature. After ½h water (2ml) was added and the dichloromethane solution was washed successively with 1M hydrochloric acid, water, saturated sodium bicarbonate and brine. The dichloromethane solution was dried, filtered, evaporated and purified on flash silica eluting with ethyl acetate:hexane (33:67), to give the title compound as a colourless viscous glass.

Example 30



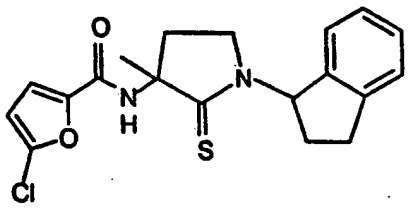
(S,R)-3-[(6-Chloropyridin-2-yl)carboxamido]-1-(1-indanyl)-3-methylpyrrolidin-2-thione.

Mp. °C: 158°

MS: [M+H] 385, 387

The reaction between 6-chloropyridine-2-carbonyl chloride (0.11g) and (S,R)-3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione hydrochloride (0.16g) was carried out as described in example 29(iv). The product was purified on flash silica eluting with ethyl acetate:hexane (33:67), to give the title compound as a off white solid of mp. 158°C.

Example 31



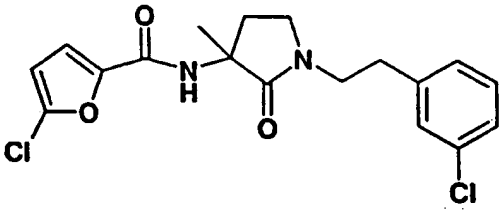
(S,R)-3-[(5-Chlorofuran-2-yl)carboxamido]-1-(1-indanyl)-3-methylpyrrolidin-2-thione.

Mp. °C: glass

MS: [M+H] 375, 377

A mixture of 2-chloro-1-methylpyridinium iodide (0.18g), 5-chlorofuroic acid (0.10g), and dry triethylamine (0.21g) in dry dichloromethane (2ml) was stirred at room temperature for 1h. Solid (S,R)-3-amino-1-(1-indanyl)-3-methylpyrrolidin-2-thione hydrochloride (0.20g) was then added. The reaction mixture was stirred at room temperature for 2h, then washed with a saturated solution of bicarbonate and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated. The residual oil was purified on flash silica eluting with ethyl acetate:hexane 25:75 to give the title product as colourless viscous glass.

Example 32



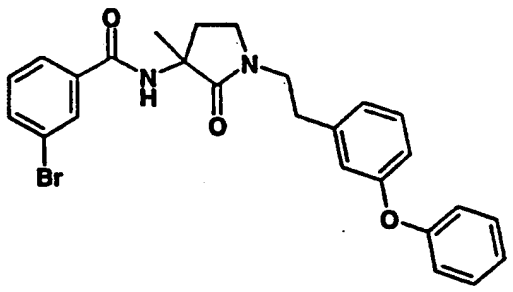
3-[(5-Chlorofuran-2-yl)carboxamido]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one.

Mp. °C: 137-138

MS: [M+H] 381, 383, 385

Following the procedure described in example 31, the title compound was prepared from 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-one (0.25g) and 5-chloro-2-furoic acid (0.15g). The crude product was purified on flash silica eluting with ethyl acetate:hexane (1:1, then 3:2), to give the title compound as a solid, m.p. 137-138°C.

Example 33



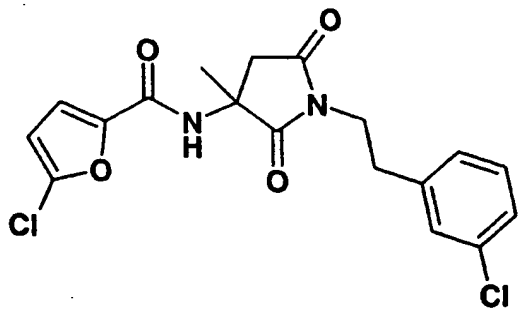
3-[(3-Bromobenzoyl)amino]-1-(3-phenoxyphenethyl)-3-methylpyrrolidin-2-one

Mp. °C: 125-127

MS: [M+H] 493, 495

The reaction between methyl N-(3-bromobenzoyl)-α-(2-oxoethyl)alanine (0.32g) and 3-phenoxyphenethylamine (0.22g) was followed by reduction with sodium borohydride (0.07g) and was carried out as described in example 3(iii). The crude oil was purified on flash silica eluting with ethyl acetate:hexane 2:1 to give the title compound as a solid, m.p. 125-127°C.

Example 34



3-[(5-Chlorofuran-2-yl)carboxamido]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2,5-dione.

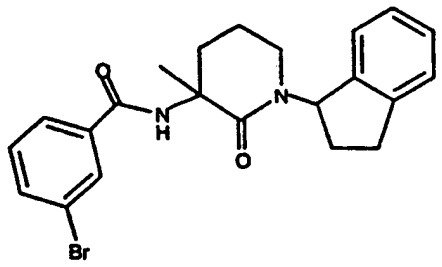
Mp. °C: 133-134

MS: [M+H] 395, 397, 399

Following the procedure described in example 31, the title compound was prepared from 3-amino-1-(3-chlorophenethyl)-3-methylpyrrolidin-2,5-dione (0.2g) and 5-chloro-2-furoic acid

(0.11g). The crude product was purified on flash silica eluting with ethyl acetate:hexane (1:1), to give the title compound as a solid, m.p. 133-134°C.

Example 35



rel-(R,S)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methyl-2-piperidone.

Mp. °C: Oil

MS: [M+H] 427, 429

i) A mixture of N-[(diphenylmethylene)glycine methyl ester (10g), anhydrous potassium carbonate (27.2g), tetrabutylammonium bromide (2.5g) and 4-bromobut-1-ene (18.4g) was heated at reflux under an atmosphere of nitrogen in acetonitrile (120ml) for 10h. The reaction mixture was cooled to 0°C, filtered, washed collected solids with diethylether and evaporated the filtrate to give an oil. The oil was taken up in diethylether and the precipitate filtered. The filtrate was evaporated to give methyl 2-[(diphenylmethylene)amino]hex-5-enoate as an oil.

ii) A stirred solution of methyl 2-[(diphenylmethylene)amino]hex-5-enoate (26.4g) in dried tetrahydrofuran (300ml) was cooled to -78°C under nitrogen and a solution of potassium bis(trimethylsilylamide) in toluene (0.5M, 164ml) was added dropwise. After stirring at -78°C for 45 minutes, a solution of iodomethane (10.2ml) in dried tetrahydrofuran (20ml) was added dropwise and the reaction mixture was allowed to warm slowly to room temperature. The resulting suspension was diluted with diethylether, filtered and evaporated to give methyl 2-[(diphenylmethylene)amino]-2-methylhex-5-enoate as an oil.

iii) A solution of methyl 2-[(diphenylmethylene)amino]-2-methylhex-5-enoate (26.5g) in aqueous citric acid (15%, 120ml) and tetrahydrofuran (130ml) was stirred at room

temperature under nitrogen for 21h. The reaction mixture was washed with diethylether (40ml, 5x), the aqueous phase was saturated with sodium chloride and cooled to 0 C. Aqueous sodium hydroxide (50%) was added to the stirred aqueous phase until pH >10, the aqueous phase was then extracted with diethylether (4x) and the combined extracts dried over magnesium sulphate, filtered and evaporated to give methyl 2-amino-2-methylhex-5-enoate as an oil.

iv) A solution of methyl 2-amino-2-methylhex-5-enoate (9.83g), phthalic anhydride (9.27g) and triethylamine (0.63g) in toluene (150ml) was heated at reflux under nitrogen with azeotroping of water. After 6h, the reaction was cooled and solvent evaporated to give an oil. The oil was dissolved in diethylether and washed with 2M hydrochloric acid, water (2x), a saturated solution of sodium bicarbonate, water (2x) and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated to give methyl 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-2-methylhex-5-enoate as an oil.

v) To a stirred solution of methyl 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-2-methylhex-5-enoate (1.05g) in a mixture of dioxan (8ml) and water (3ml) containing a crystal of osmium tetroxide, was added portionwise over ½h a solution of sodium periodate (1.32g) in water (9ml). After 1½h the reaction was diluted with water and extracted with diethylether (2x). The combined extracts were washed with aqueous sodium metabisulphite (10%), water, brine, dried over magnesium sulphate, filtered and evaporated to an oil. The crude oil was purified on flash silica eluting with diethylether:hexane (3:2) then diethylether to give methyl 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-formyl-2-methylbutanoate as an oil.

vi) A mixture of methyl 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-4-formyl-2-methylbutanoate (1.68g), 1-aminoindane (0.85g), sodium acetate (0.95g) and sodium cyanoborohydride (0.73g) in dried tetrahydrofuran (20ml) was stirred over baked molecular sieves (4Å, 5.8g) at room temperature. After 4h, the reaction mixture was acidified with 2M hydrochloric acid, then basified with 2M sodium carbonate and extracted (2x) with diethylether. The combined extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to a red oil. The crude oil was purified on flash chromatography eluting with dichloromethane:methanol (99:1, then 98:2) to give methyl 2-

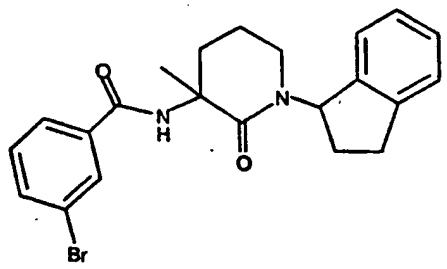
(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-5-(indan-1-amino)-2-methylpentanoate as an oil.

vii) To a stirred solution of methyl 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-5-(indan-1-amino)-2-methylpentanoate (0.62g) in dried toluene (100ml) at room temperature under nitrogen, was added a solution of trimethylaluminium in toluene (2M, 0.77ml). The solution was heated to 75°C for 5h, then cooled to 0°C and 2M hydrochloric acid was added dropwise. The mixture was stirred at room temperature for 1½h then washed with 2M hydrochloric acid, water and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated to an oil. The crude oil was purified on flash chromatography to give 3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-(1-indanyl)-3-methylpiperidone as an oil.

viii) A solution of 3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-(1-indanyl)-3-methylpiperidone (0.11g) and hydrazine monohydrate (0.02g)in ethanol (4ml) was heated at reflux under nitrogen for 6h. The reaction mixture was cooled, filtered and evaporated to an oil. The oil was taken up in chloroform and the fine suspension filtered through a pad of celite. The filtrate was evaporated to give 3-amino-1-(1-indanyl)-3-methyl-2-piperidone as an oil.

ix) A mixture of 3-amino-1-(1-indanyl)-3-methyl-2-piperidone (0.05g), 3-bromobenzoyl chloride (0.05g) and dried triethylamine (0.23ml) in dried dichloromethane (3ml) was stirred under nitrogen at room temperature. After 3 hours the mixture was diluted with dichloromethane, washed with water (2X), brine, dired over magnesium sulphate, filtered, and evaporated to an oil. The crude diastereomeric mixture was separated on flash silica eluting with ethyl acetate:hexane (1:1). The faster eluting fractions were combined and evaporated to give the title compound as an oil.

Example 36



rel-(R,R)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methyl-2-piperidone.

Mp. °C: Oil

MS: [M+H] 427, 429

The slower eluting fraction from the chromatography in example 36(ix) gave the title compound as an oil.

The following table (Table II) illustrates additional compounds (Examples 37-88), produced using the directed combinatorial methods, essentially as described for Example 5 above. While each of these compounds were made according to a particular directed combinatorial synthesis, the ordinarily skilled artisan will appreciate that all of these compounds could be synthesised as part of a diverse combinatorial library. The abbreviations used in the table are commmonly used in the field and would be readily appreciated by a practitioner in the field.

In Table II below , the first column gives the example number for the compound. The second column provides the structure of the exemplified compound. The next two columns describe the substitutions of the particular example compound. "ArCOOH" provides the carboxylic acid (or derivative) employed to optimize the amide functionality of the lactam product essentially as described in **Scheme V** above, wherein "Ar" is as defined previously. "Z-NH_2" provides the primary amine employed in the reductive amination of the protected aldehyde scaffold reactant as described in **Scheme VI**, wherein "Z" is as described previously. The next column, entitled "Stereo" describes the stereochemistry profile of the exemplified compound. "MW", defines the molecular weight of the compound and "MS" defines the mass of the compound as as determined by mass spectroscopy. Further, any other abbreviations used in Table II are commonly used in the field and, as such, would be readily understood by a practitioner in the field.

Table II

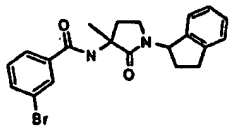
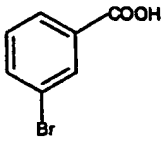
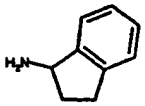
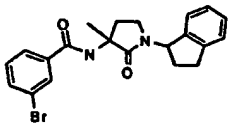
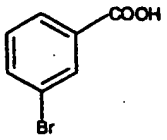
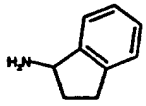
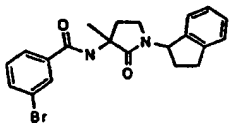
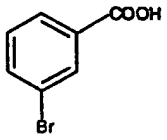
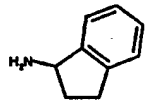
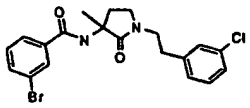
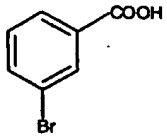
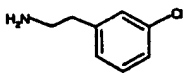
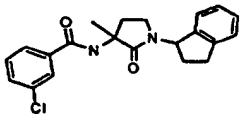
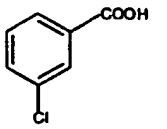
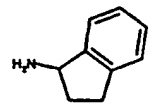
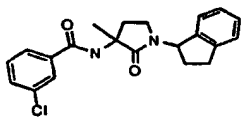
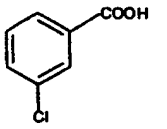
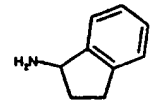
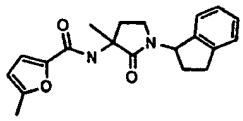
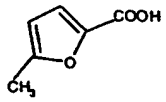
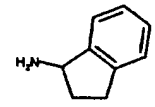
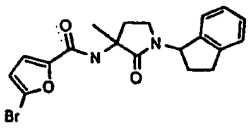
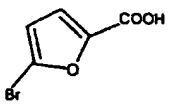
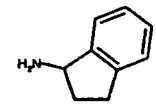
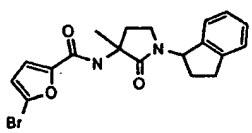
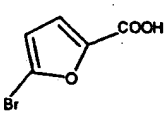
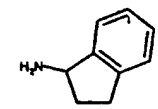
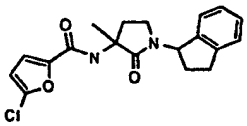
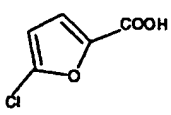
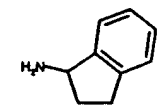
Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS
37				diastereomeric mix	412.07	414.90
37a				enantiomer pair 1	-	414.90
37b				enantiomer pair 2	-	415.00
38				racemic	434.03	434.9 436.9
39				enantiomer pair 1	368.12	369.00
39a				enantiomer pair 2	-	369.0 371.0
40				enantiomer pair 2	338.16	339.00
41				enantiomer pair 1	402.06	402.90
41a				enantiomer pair 2	-	402.90
42				enantiomer pair 2	358.11	359.0 361.0

Table II

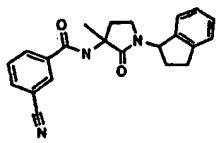
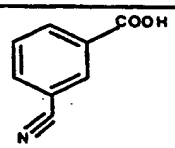
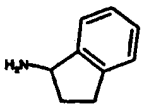
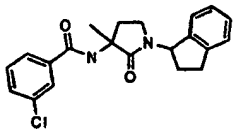
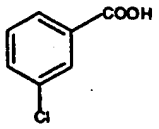
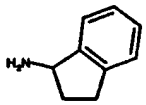
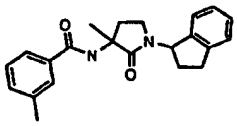
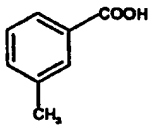
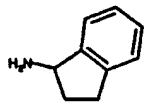
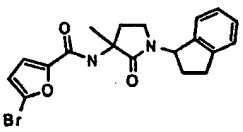
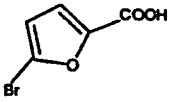
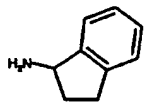
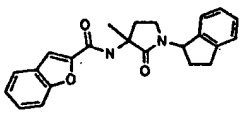
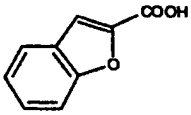
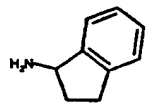
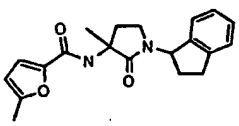
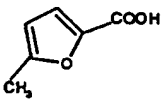
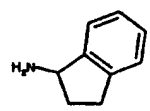
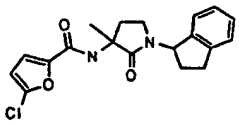
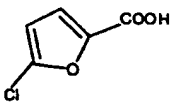
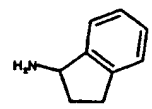
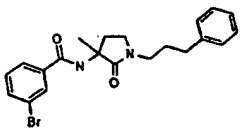
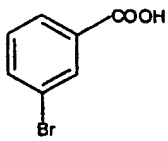
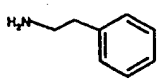
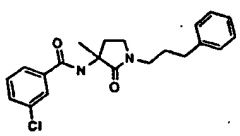
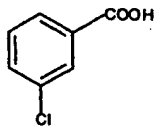
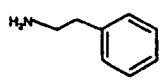
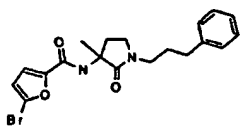
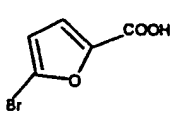
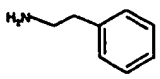
Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS
43				enantiomer pair 2	359.16	360.10
44				enantiomer pair 2	368.13	369.00
45				enantiomer pair 2	348.18	349.10
46				enantiomer pair 2	402.06	402.90
47				enantiomer pair 2	374.16	375.10
48				enantiomer pair 2	338.16	339.10
49				enantiomer pair 2	358.11	359.00
50				racemic	414.09	417.00
51				racemic	370.14	371.00
52				racemic	404.07	406.90

Table II

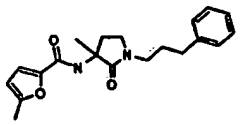
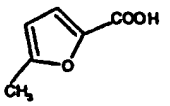
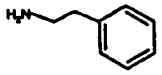
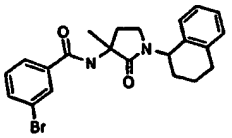
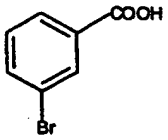
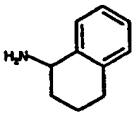
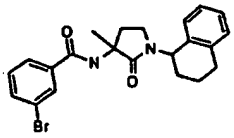
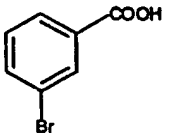
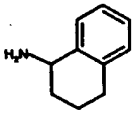
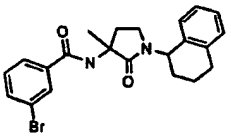
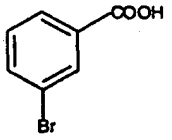
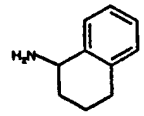
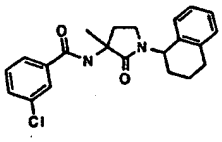
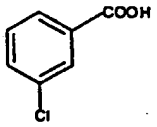
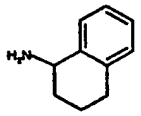
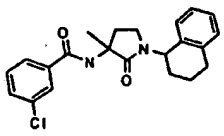
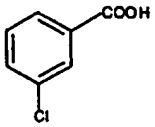
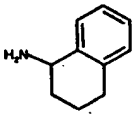
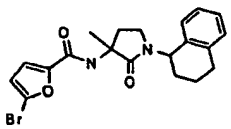
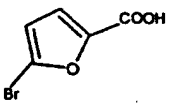
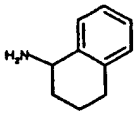
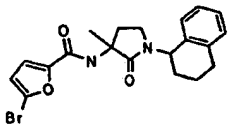
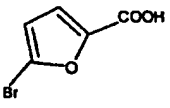
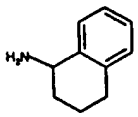
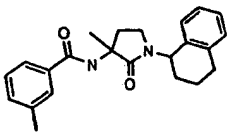
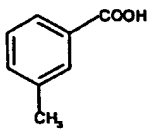
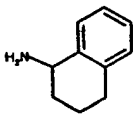
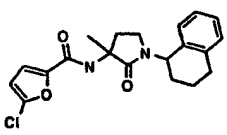
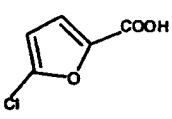
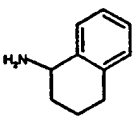
Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS
53				racemic	340.18	341.10
54				racemic diastereomers	426.09	
54a				enantiomer pair 1	426.09	427 429
54b				enantiomer pair 2	426.09	427.0 429.0
55				enantiomer pair 1	382.14	383.00
55a				enantiomer pair 2	"	383.10
56				enantiomer pair 1	416.07	418.90
56a				enantiomer pair 2	"	417.00
57				enantiomer pair 2	362.20	363.10
58				enantiomer pair 2	372.12	373.00

Table II

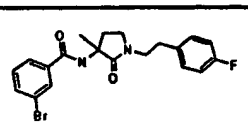
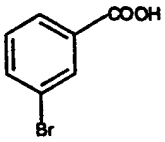
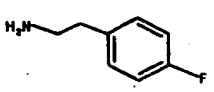
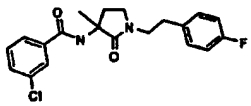
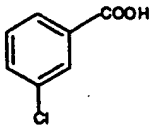
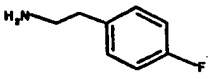
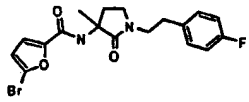
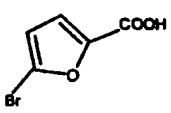
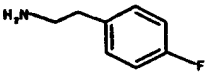
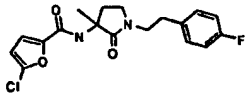
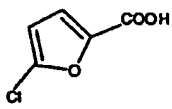
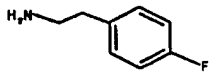
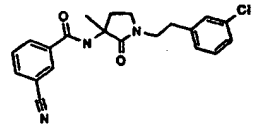
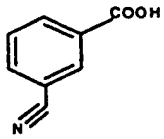
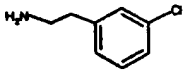
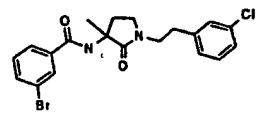
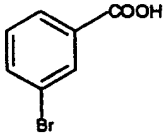
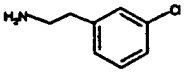
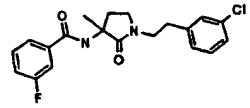
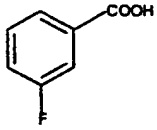
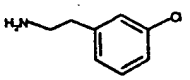
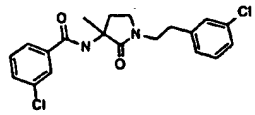
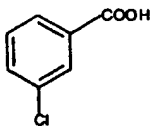
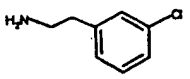
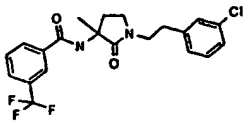
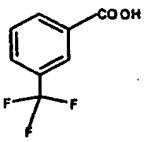
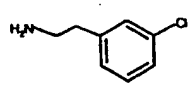
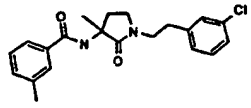
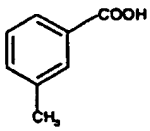
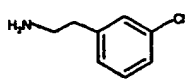
Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS
59				racemic	418.07	418.90
60				racemic	374.12	375.00
61				racemic	408.05	408.90
62				racemic	364.10	365.00
63				racemic	381.12	382.00
64				racemic	434.04	434.9 436.9
65				racemic	374.12	375.00
66				racemic	390.09	391.0 393.0
67				racemic	424.12	425.00
68				racemic	370.14	371.00

Table II

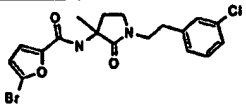
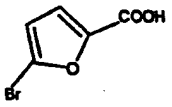
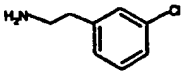
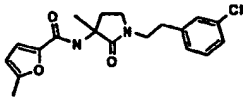
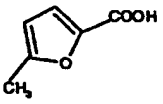
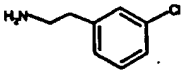
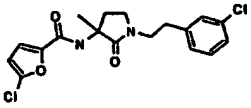
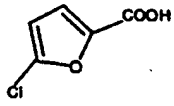
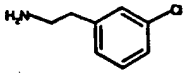
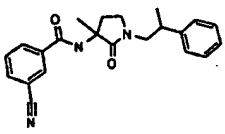
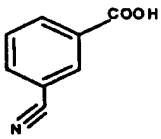
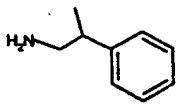
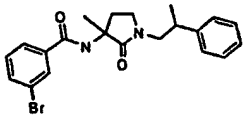
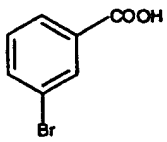
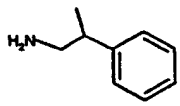
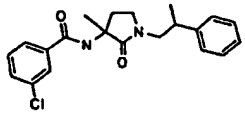
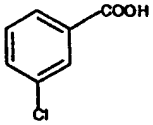
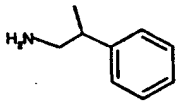
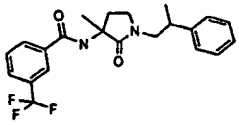
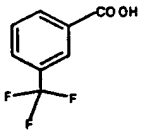
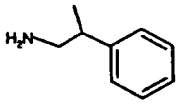
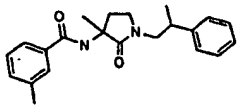
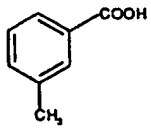
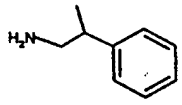
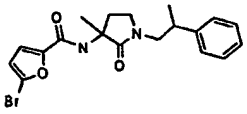
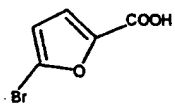
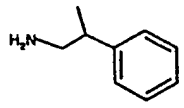
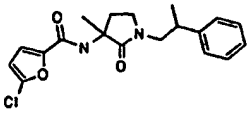
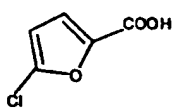
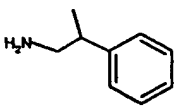
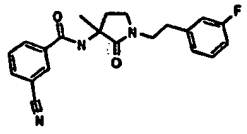
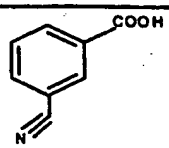
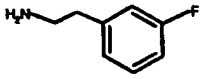
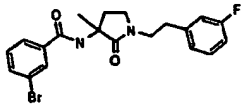
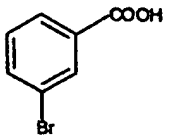
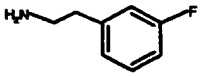
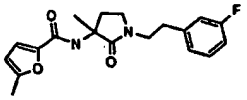
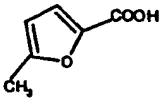
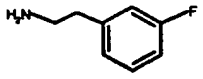
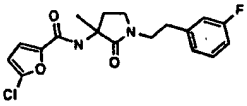
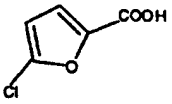
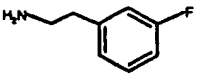
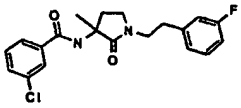
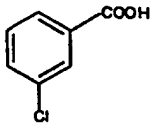
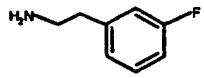
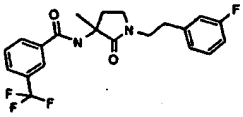
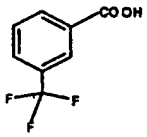
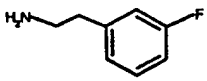
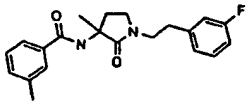
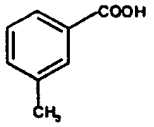
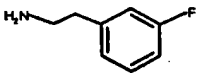
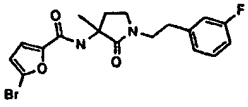
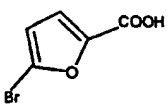
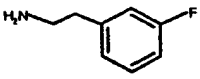
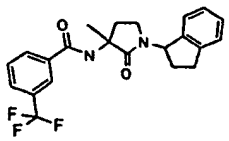
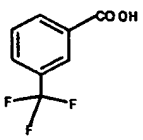
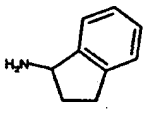
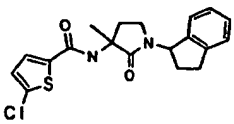
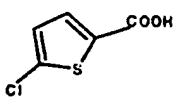
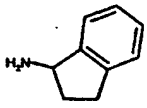
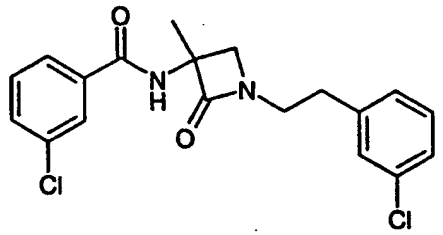
Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS
69				racemic	424.02	424.9 426.9
70				racemic	360.12	361.00
71				racemic	380.07	381.0 382.9
72				racemic	361.18	362.10
73				racemic	414.09	415.00
74				racemic	370.14	371.10
75				racemic	404.17	405.10
76				racemic	350.20	351.10
77				racemic	404.07	404.90
78				racemic	360.12	361.00

Table II

Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS
79				racemic	365.15	366.00
80				racemic	418.07	418.9 420.9
81				racemic	344.15	345.00
82				racemic	364.10	365.00
83				racemic	374.12	375.00
84				racemic	408.40	409.00
85				racemic	354.17	355.10
86				racemic	408.05	408.9 410.9
87				enantiomer pair 2	402.15	403.00
88				enantiomer pair 2	374.08	375.00

Example 89



3-Chloro-N-{1-[2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-azetidinyl}benzamide

Mp. °C: 98-99

MS: [M+H] 377, 379

Method 1

i) Triethylamine (11 mmol) and chloroacetonitrile (11 mmol) were added to a solution of 3-chlorophenethylamine (10 mmol) in ethanol (30 ml) and the reaction mixture heated under reflux for 4 hours. The mixture was evaporated to a small volume, diluted with ethyl acetate (40 ml) and washed with water (2 x 30 ml) and brine (30 ml). The organic layer was separated, dried over sodium sulphate and evaporated *in vacuo*. The product was purified by column chromatography (silica, $CHCl_3$: acetone 20:1) to give (2-(3-chlorophenyl)ethylamino)acetonitrile as a liquid.

ii) To a stirred solution of diisopropylamine (45 mmol) and tetrahydrofuran (100 ml) cooled in a dry ice acetone bath, n-butyl lithium (43 mmol) was added. After one hour, a solution of (N-tert-butoxy-carbonyl)-L-alanine methyl ester (21.6 mmol) in anhydrous THF (40 ml) was added to the cooled reaction mixture. After one hour, a solution of (2-(3-chlorophenyl)ethylamino)acetonitrile (10.8 mmol) in anhydrous THF (30 ml) was added to the cooled mixture. After a further one hour at -78° C., the mixture was allowed to warm to room temperature and stirred for another 16 hours. The reaction mixture was quenched with aqueous saturated ammonium chloride, diluted with iced water and then extracted with $CHCl_3$. The organic layer was separated, dried over sodium sulphate and evaporated *in vacuo*. The crude oil was purified by column chromatography twice (silica; hexane:ethyl acetate 1:1) to give tert-butyl 1-[2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-azetidinylcarbamate as an oil that solidified on standing.

iii) Trifluoroacetic acid (0.1 ml) was added to a stirred solution of tert-butyl 1-[2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-azetidinylcarbamate (50 mg, 0.15 mmol) in CH_2Cl_2 (0.5 ml) and anisole (50 mg). After 30 minutes at room temperature, the solution was evaporated and the residual oil was triturated with diethyl ether (0.2 ml), n-hexane (0.4 ml). The mixture was decanted to leave 3-amino-1-[2-(3-chlorophenyl)ethyl]-3-methyl-2-azetidinone trifluoroacetate as a viscous oil MS: [M+H] 239, 241.

iv) A solution of 3-amino-1-[2-(3-chlorophenyl)ethyl]-3-methyl-2-azetidinone trifluoroacetate (35 mg) in dried CH_2Cl_2 (0.5 ml) was added after one hour to a stirred mixture of 3-chlorobenzoic acid (15.7 mg, 0.1 mmol), 2-chloro-1-methylpyridinium iodide (25.5 mg, 0.1 mmol) and triethylamine (20 mg, 0.2 mmol) in dry CH_2Cl_2 (0.5 ml) at room temperature. After 2 hours, saturated aqueous sodium bicarbonate (1 ml) was added. The CH_2Cl_2 solution was washed with aq$NaHCO_3$ (3 x 1 ml), brine (1 ml), dried, filtered and evaporated to a viscous oil. The product was purified by chromatography on flash silica (Et_2O then EtOAc) to give the title product as a white solid.

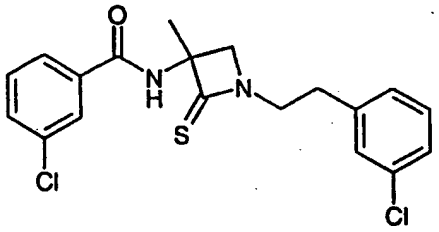
Method 2

i) 3-Chlorobenzoyl chloride (9.34 g, 53.4 mmol) was added dropwise to a stirred solution of D,L-alanine methyl ester (5 g, 48.5 mmol) and triethylamine (8.1 ml, 58.2 mmol) in CH_2Cl_2 (100 ml) cooled in an ice bath. After 30 minutes, allowed to warm to room temperature for 30 minutes. The reaction mixture was washed with water and brine then dried, filtered and evaporated to a yellow oil (11.23 g). The product was purified by chromatography on flash silica (EtOAc:hexane 1:3) to give methyl 2-[(3-chlorobenzoyl)amino]propanoate as a colourless oil.

ii) n-Butyl lithium (2.5 M in hexane, 31.2 ml, 78 mmol) was added to a stirred solution of diisopropylamine (8.14 g, 81 mmol) in dried THF (70 ml) cooled to -78° C. After one hour, a solution of methyl 2-[3-chlorobenzoyl)amino]-propanoate (6.30 g, 26 mmol) in THF (50 ml) was added dropwise. After 1.5 hours at 78° C. a solution of (2-(3-chlorophenyl)ethylamino)acetonitrile (5.05 g, 26 mmol) in THF (50 ml)

was added and the mixture stirred for 2 hours before allowing to warm to room temperature. The reaction was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate. The ethyl acetate solution was washed with water, brine, dried, filtered and evaporated to an orange oil. The crude product was purified by flash chromatography (EtOAc:hexane 1:4 then 1:1) to give the title product as a viscous oil (2.65 g). A sample crystallised from EtOAc:hexane 1:2 as a white solid.

Example 90



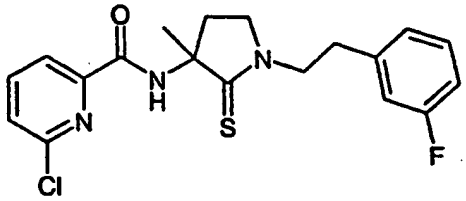
3-Chloro-N{1-[2-(3-chlorophenyl)ethyl]-3-methyl-2-thioxo-3-azetidinyl}benzamide

Mp. °C: glass

MS: [M+H] 393; 395

Lawessons reagent (301 mg, 0.745 mmol) was added to a stirred solution of 3-chloro-N-{1-[2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-azetidinyl}benzamide (500 mg, 1.33 mmol) in toluene and the mixture heated under reflux for 2 hours. The solvent was evaporated and the residue chromatographed on flash silica (CH_2Cl_2 then 10% Et_2O in CH_2Cl_2) and further purified by chromatography (EtOAc:hexane 1:1) to give the title product as a glass.

Example 91



3-(6-Chloropyridine-2-carboxamido)-1-(3-fluorophenethyl)-3-methylpyrrolidine-2-thione

Mp.° C: 89-90

MS: (M+H] 392, 394

i) A solution of 2-(3-fluorophenyl)ethylamine (13.3 g, 95 mmol) and methyl N-(t-butoxycarbonyl)-α- (2-oxoethyl)alanine (23.4 g, 95 mmol) in methanol (200 ml) was stirred at room temperature under nitrogen atmosphere for 1.5 hours. The mixture was then cooled and solid sodium borohydride (7.19 g, 0.19 mol) added portionwise allowing effervescence to subside between additions. After 1.5 hours, the reaction was quenched with water (300 ml) and extracted with diethyl ether (2 x 300 ml). The ether extracts were washed with 2 M aqueous hydrochloric acid, water, brine, dried, filtered and evaporated to a yellow oil of 3-[N-(tert-butoxycarbonyl)amino]-1-(3-fluorophenethyl)-3-methyl-pyrrolidin-2-one that solidified on standing.

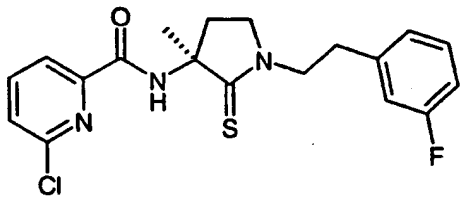
ii) Lawessons reagent (17.48 g, 43.2 mmol) was added to a stirred solution of 3-[N-tert-butoxycarbonyl)amino]-1-(3-fluorophenethyl)-3-methylpyrrolidin-2-one (26.4 g, 78.6 mmol) in toluene (100 ml). After 2 hours heating under reflux, the mixture was evaporated to a red oil. The crude product was purified by chromatography on flash silica eluting with dichloromethane to give 3-[N-tert-butoxycarbonyl)amino]-1-(3-fluorophenethyl)-3-methylpyrrolidine-2-thione as an oil.

iii) A solution of 3-[N-(tert-butoxycarbonyl)amino}-1-(3-fluorophenethyl)-3-methylpyrrolidine-2-thione (16.2 g, 46.2 mmol) in dioxan-HCl (4 M, 100 ml) was stirred at room temperature for 16 hours. The reaction mixture was evaporated and the residue dissolved in dioxan (20 ml). Diethyl ether (30 ml) was added and the

product crystallised with cooling in the fridge to give 3-amino-1-(3-fluorophenethyl)-3-methylpyrrolidone-2-thione hydrochloride as a solid.

iv) A solution of 6-chloro-2-pyridinecarbonyl chloride (6.04 g, 34 mmol) in dichloromethane was added to a stirred solution of 3-amino-1-(3-fluorophenethyl)-3-methylpyrrolidine-2-thione hydrochloride (9.00 g, 31.2 mmol) and triethylamine (13 ml, 93.6 mmol) in dichloromethane (50 ml) at room temperature. After 3 hours the organic phase was washed with water, saturated aqueous sodium hydrogen carbonate, 2 M hydrochloric acid, brine, dried, filtered and evaporated to a red oil (12.1 g). The crude product was purified by column chromatography on flash silica eluting with diethyl ether followed by crystallisation from isopropyl alcohol to give the title product as a white solid.

Example 92



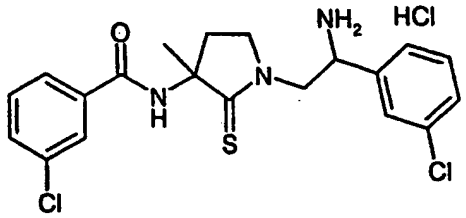
(S)-3-(6-Chloropyridine-2-carboxamido)-1-(3-fluorophenethyl)-3-methylpyrrolidine-2-thione

Mp. ° C: 120-121

MS: (M+H] 392, 394

The title compound was separated from the racemate by preparative chiral HPLC on a 250 x 20 mm id chiracel-OD column using hexane:isopropanol 1:1 and collecting the first eluting enantiomer. The second eluting enantiomer was assigned (R)-configuration by xray structure analysis of crystals grown from ethyl acetate-hexane.

Example 93



Diastereoisomer 1: N-{1-[2-amino-2-(3-chlorophenyl)ethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide hydrochloride salt.

MS: [M+H] 422, 424

i) Aminodiphenylmethane (9.36 g) was added to a stirred solution of methyl N-(t-butoxycarbonyl)-α-(2-oxoethyl)alanine (11.92 g) in methanol (100 ml) at room temperature under an atmosphere of nitrogen. After one hour, the reaction mixture was cooled to 0° C. and sodium borohydride (3.71 g) added portionwise. After addition, the reaction mixture was stirred at room temperature for 0.5 hours, concentrated *in vacuo*, diluted with water and extracted twice with diethyl ether. The combined extracts were washed with water and brine, dried over magnesium sulphate, filtered and evaporated to give methyl 2-(t-butoxycarbonyl)amino-4-(diphenylmethyl)amino-2-methylbutanoate as an oil.

ii) A solution of methyl 2-(t-butoxycarbonyl)amino-4-(diphenylmethyl)amino-2-methylbutanoate (18.0 g) in methanol (200 ml) was hydrogenolysed over 10% palladium on carbon (3.0 g) at 70 psi for 2 days. The reaction mixture was filtered through celite and evaporated. The crude was crystallised from a mixture of cyclohexane and hexane to give 3-(t-butoxycarbonyl) amino-3-methylpyrrolidin-2-one as a colourless solid.

iii) A suspension of 3-(t-butoxycarbonyl)amino-3-methylpyrrolidin-2-one (1.64 g) and 2,4-bis-(4-methoxyphenyl-1,3-dithia-2,4-diphosphetane-2,4-disulphide (1.61 g) in toluene (40 ml) was heated at reflux for 1 hour. The clear reaction mixture was cooled and evaporated to give a solid. The crude was purified on flash silica eluting

with dichloromethane, dichloromethane-diethyl ether (19:1 and then 4:1) to give 3-(t-butoxycarbonyl)amino-3-methylpyrrolidin-2-thione as a colourless solid.

iv) A mixture of powdered sodium hydroxide (45 mg), 3-(t-butoxycarbonyl)amino-3-methylpyrrolidin-2-thione (1.73 g) and methyl 2-(3-chlorophenyl)propenoate (1.82 g) in tetrahydrofuran (20 ml) was stirred at room temperature under an atmosphere of nitrogen overnight. The reaction mixture was neutralised with aqueous hydrochloric acid (2 M), concentrated *in vacuo* and diluted with water. The concentrate was extracted twice with diethyl ether and the combined extracts dried over magnesium sulphate, filtered and evaporated to give methyl 3-{3-[(t-butoxycarbonyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-2-(3-chlorophenyl)propanoate as an oil.

v) A solution of hydrogen chloride in dioxan (4 M, 10 ml) was added to a stirred solution of methyl 3-{3-[(t-butoxycarbonyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-2-(3-chlorophenyl)propanoate (1.05 g) in dioxan (2 ml) at room temperature. After one hour, the reaction mixture was evaporated to give methyl 3-(3-amino-3-methyl-2-thioxo-1-pyrrolidinyl)-2-(3-chlorophenyl)propanoate hydrochloride salt as a colourless solid,

vi) A mixture of methyl 3-(3-amino-3-methyl-2-thioxo-1-pyrrolidinyl)-2-(3-chlorophenyl)propanoate hydrochloride salt (0.89 g), triethylamine (0.75 g) and 3-chlorobenzoyl chloride (0.47 g) in dichloromethane (20 ml) was stirred at room temperature for 45 minutes. The reaction mixture was washed with aqueous hydrochloric acid (2 M), water and brine, dried over magnesium sulphate, filtered and evaporated to give methyl 3-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-2-(3-chlorophenyl)propanoate as an oil.

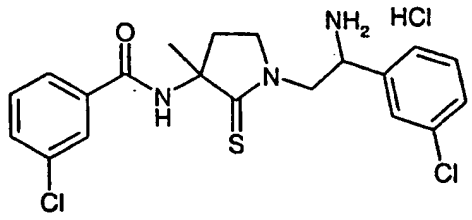
vii) A solution of methyl 3-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-2-(3-chlorophenyl)propanoate (0.48 g) and lithium hydroxide (0.22 g) in a mixture of methanol (30 ml) and water (10 ml) was stirred under an atmosphere of nitrogen at 0° C. for 7 hours. The reaction mixture was diluted with water and

washed once with diethyl ether. The aqueous phase was acidified with aqueous hydrochloric acid (2 M) and extracted three times with dichloromethane. The combined extracts were dried over magnesium sulphate, filtered and evaporated to give 3-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-2-(3-chlorophenyl)propanoic acid as a colourless foam.

viii) A mixture of 3-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-2-(3-chlorophenyl)propionic acid (0.35 g), diphenylphosphoric azide (0.16 g) and dried triethylamine (94 mg) in dried t-butanol (10 ml) was heated at reflux for 4 hours. The reaction mixture was cooled, evaporated and the residue purified on flash silica eluting with diethyl ether to give t-butyl 2-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-1-(3-chlorophenyl)ethylcarbamate as a colourless foam. The mixture of diastereoisomers was separated by preparative HPLC on a 250 x 20 mm id. KR60-5S1L column eluting at ambient temperature with hexane:dichloromethane:ethanol (73.5: 24.5: 2) at a flow rate of 20 ml/min to give diastereoisomer 1 and diastereoisomer 2 as colourless solids.

ix) Diastereoisomer 1, t-butyl 2-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-1-(3-chlorophenyl)ethylcarbamate (152 mg) was dissolved in a solution of hydrogen chloride in dioxan (4 M, 0.5 ml) and stirred at room temperature for 2 hours. The reaction mixture was evaporated and the residue triturated with diethyl ether to give the title compound as a solid.

Example 94

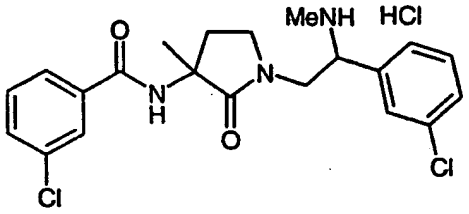


Diastereoisomer 2: N-{1-[2-amino-2-(3-chlorophenyl)ethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide hydrochloride salt

MS: [M+H] 422, 424

The title compound was prepared as a colourless solid from t-butyl 2-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-1-(3-chlorophenyl)ethylcarbamate (170 mg) isolated as diastereoisomer 2 in Example 93 (viii) by the procedure described in Example 93 (ix).

Example 95



Mp. ° C: 118-120

MS: [M+H] 419, 421

i) A suspension of 3-(t-butoxycarbonyl)amino-3-methyl pyrrolidin-2-one (2.47 g) and trimethyloxonium fluoroborate (3.41 g) in dried dichloromethane (80 ml) was stirred at room temperature under an atmosphere of nitrogen for 24 hours. Cold aqueous potassium carbonate (10%, 15 ml) was added and the suspension filtered. The filtrate was separated and the organic phase dried over magnesium sulphate, filtered and evaporated to give t-butyl 5-methoxy-4-methyl-3,4-dihydro-2H-pyrrol-4-ylcarbamate as a colourless oil.

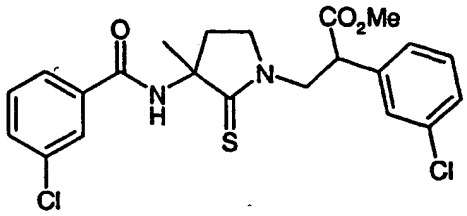
ii) A solution of t-butyl 5-methoxy-4-methyl-3,4-dihydro-2H-pyrrol-4-ylcarbamate (1.9 g) and 3-chloro-2-bromoacetophenone (2.14 g) in dried dimethylformamide (12 ml) was stirred at 60° C. under an atmosphere of nitrogen overnight. The reaction mixture was cooled, diluted with water and extracted with dichloromethane. The extract was washed three times with water and brine, dried over magnesium sulphate, filtered and evaporated to a red oil. The crude was purified on flash silica eluting with ethyl acetate-hexane (3:2) to give t-butyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinylcarbamate as a yellow solid.

iii) t-Butyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinyl carbamate (0.70 g) was dissolved in a solution of hydrogen chloride in dioxan (4 M, 5 ml). The solution was stirred at room temperature for 2 hours giving a yellow suspension. The suspension was diluted with diethyl ether and filtered to give 3-amino-1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methylpyrrolidin-2-one hydrochloride salt as a yellow solid.

iv) To a stirred solution of 3-amino-1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methylpyrrolidin-2-one hydrochloride (0.52 g) and triethylamine (0.4 g) in dichloromethane (20 ml) at room temperature was added a solution of 3-chlorobenzoylchloride (0.32 g) in dichloromethane (5 ml) dropwise. After stirring for 2 hours, the reaction mixture was washed with aqueous hydrochloric acid (2 M), twice with water and brine, dried over magnesium sulphate, filtered and evaporated to a foam. Trituration with diethyl ether and filtration gave N-{1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinyl}-3-chlorobenzamide as a colourless solid.

v) To a stirred solution of N-{1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinyl}3-chlorobenzamide (200 mg) in dried tetrahydrofuran (2 ml) was added a solution of methylamine in tetrahydrofuran (2M, 0.27 ml) followed by sodium triacetoxyborohydride (158 mg) and acetic acid (28 µl). The mixture was stirred at room temperature under an atmosphere of nitrogen for 3 days, then diluted with aqueous hydrochloric acid (2 M) and washed twice with diethyl ether. The aqueous phase was made basic with a saturated solution of sodium bicarbonate and extracted twice with dichloromethane. The combined extracts were washed twice with water, brine and dried over magnesium sulphate, filtered and evaporated to give a colourless oil. Crystallised from diethyl ether-hexane to give the title compound as a colourless solid.

Example 96



Methyl 3-{3-[(3-chlorobenzoyl)amino]-3-methyl-2-thioxo-1-pyrrolidinyl}-2-(3-chlorophenyl)propanoate

MS: [M+H] 465, 467

The title compound was prepared by the method described in Example 93 (vi).

Examples 97 – 120

The following table (Table III) illustrates additional compounds (Examples 97 – 120), produced using the directed combinatorial methods, essentially as described for Example 5 above. The abbreviations used in the table are commmonly used in the field and would be readily appreciated by a practitioner in the field.

In the Table III below, the first column gives the example number for the compound. The second column provides the structure of the exemplified compound. The next two columns describe the substitutions of the particular example compound. "ArCOOH" provides the carboxylic acid (or derivative) employed to optimize the amide functionality of the thiolactam product essentially as described in **Scheme V** above, wherein "Ar" is as defined previously. "Z-NH_2" provides the primary amine employed in the reductive amination of the protected aldehyde scaffold reactant as described in **Scheme VI**, wherein "Z" is as described previously. The next column, entitled "Stereo" describes the stereochemistry profile of the exemplified compound. "MW", defines the molecular weight of the compound and "MS" defines the mass of the compound as as determined by mass spectroscopy.

Table III

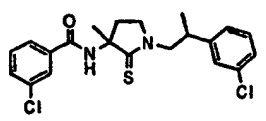
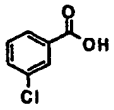
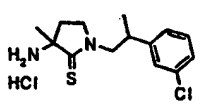
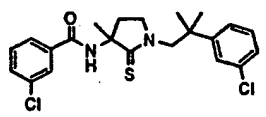
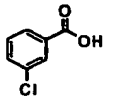
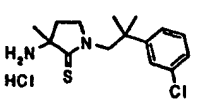
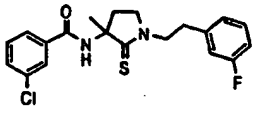
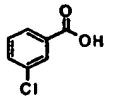
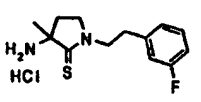
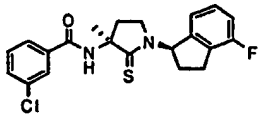
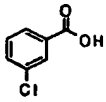
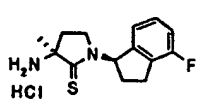
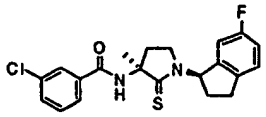
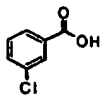
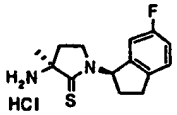
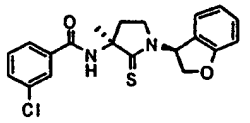
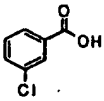
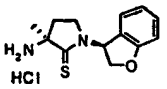
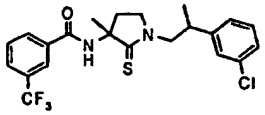
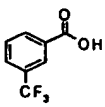
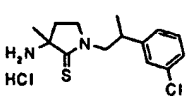
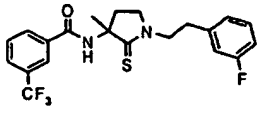
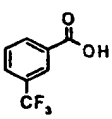
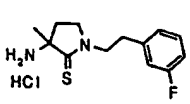
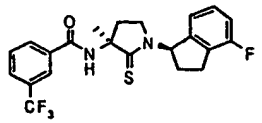
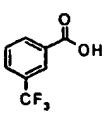
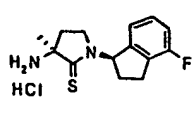
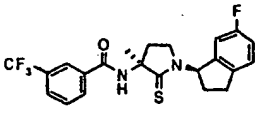
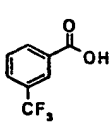
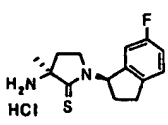
Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS [M+H]
97				diastereomeric mix	421.39	421 423
98				racemic	435.42	435 437
99				racemic	390.91	391 393
100				enantiomer pair 1	402.92	403 405
101				enantiomer pair 1	402.92	403 405
102				enantiomer pair 1	386.90	387 389
103				diastereomeric mix	454.95	455 457
104				racemic	424.46	425
105				enantiomer pair 1	436.48	437
106				enantiomer pair 1	436.48	437

Table III

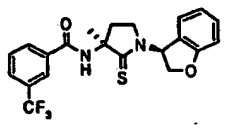
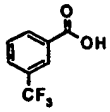
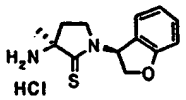
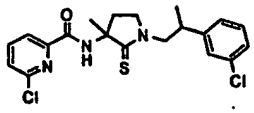
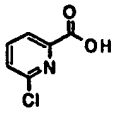
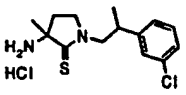
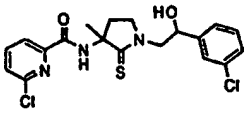
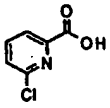
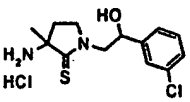
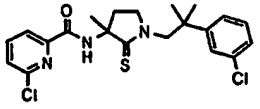
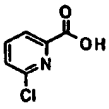
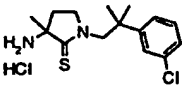
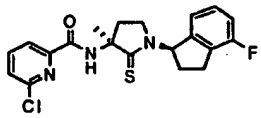
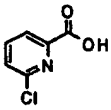
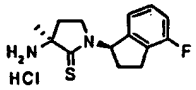
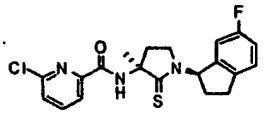
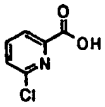
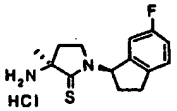
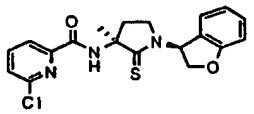
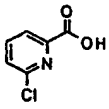
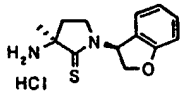
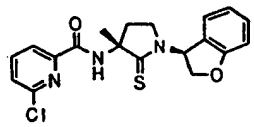
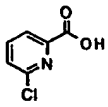
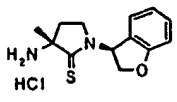
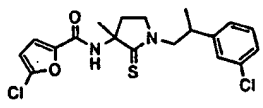
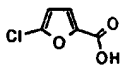
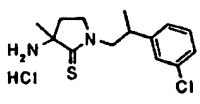
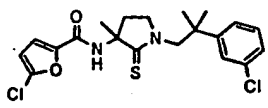
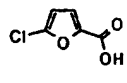
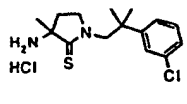
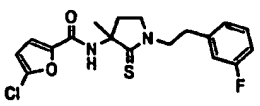
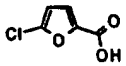
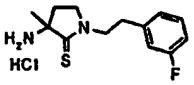
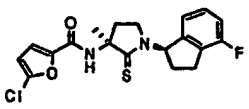
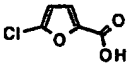
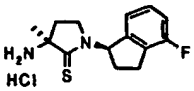
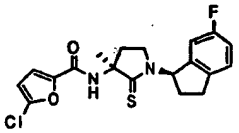
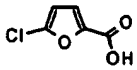
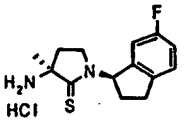
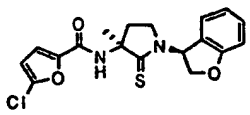
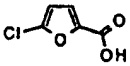
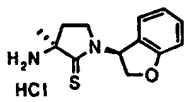
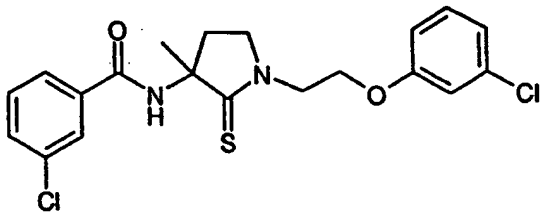
Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS [M+H]
107				enantiomer pair 1	420.46	421
108				diastereomeric mix	422.38	423 425
109				diastereomeric mix	408.29	408 410
110				racemic	436.41	436 438
111				enantiomer pair 1	403.91	404 406
112				enantiomer pair 1	403.91	404 406
113				enantiomer pair 1	387.89	388 390
114				enantiomer pair 2	387.89	388 390
115				diastereomeric mix	411.35	411 413
116				racemic	425.38	425 427

Table III

Example No.	Structure	ArCOOH	Z-NH2	Stereo	MW	MS [M+H]
117				racemic	380.87	381 383
118				enantiomer pair 1	392.88	393 395
119				enantiomer pair 1	392.88	393 395
120				enantiomer pair 1	376.86	377 379

Example 121



N-{[2-(3-chlorophenoxy)ethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide

Mp. °C: 114-115

MS: [M+H] 423 425

i) Sodium borohydride (847 mg, 22.4 mmol) was added portionwise to a stirred mixture of zirconium (IV) chloride (5.23 g, 22.4 mmol) in tetrahydrofuran (50 ml) with cooling under nitrogen atmosphere. 3-chlorophenoxy acetonitrile (3.0 g, 17.9 mmol) was added dropwise and the mixture stirred for 1h before quenching with water. The mixture was basified with 2M sodium hydoxide and extracted with diethyl ether (2 x 100 ml). The extracts were washed with water, brine, dried filtered and evaporated to a yellow liquid that was purified by bulb to bulb distillation to give 2-(3-chlorophenoxy)ethylamine.

ii) 2-(3-chlorophenoxy)ethylamine was reacted with methyl N-(t-butoxycarbonyl)-α-methyl-(2-oxoethyl)alanine as described in example 29 (i) to give 3-[N-(t-butoxycarbonyl)amino]-1-(3-chlorophenoxyethyl)-3-methylpyrrolidin-2-one as an oil.

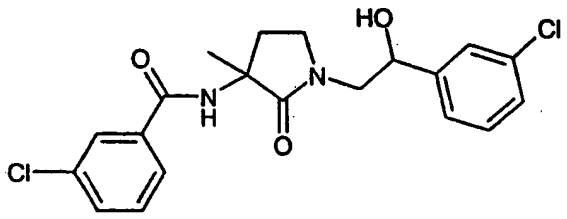
iii) 3-[N-(t-butoxycarbonyl)amino]-1-(3-chlorophenoxyethyl)-3-methylpyrrolidin-2-one was reacted with Lawessons reagent as described in example 29 (ii) to give 3-[N-(t-butoxycarbonyl)amino]-1-(3-chlorophenoxyethyl)-3-methylpyrrolidin-2-thione as an oil.

iv) 3-[N-(t-butoxycarbonyl)amino]-1-(3-chlorophenoxyethyl)-3-methylpyrrolidin-2-thione was deprotected with 4M hydrogen chloride in dioxan as described in

example 29 (iii) to give 3-amino-1-[2-(3-chlorophenoxy)ethyl]-3-methylpyrrolidin-2-thione hydrochloride.

v) 3-amino-1-[2-(3-chlorophenoxy)ethyl]-3-methylpyrrolidin-2-thione hydrochloride was reacted with 3-chlorobenzoyl chloride as described in example 29 (iv) to give the title product as a white solid.

Example 122

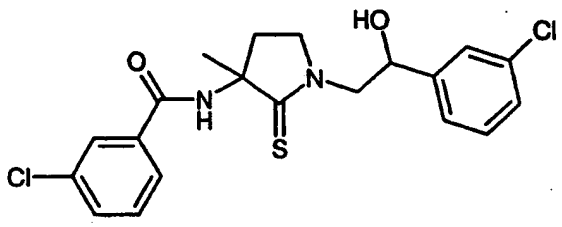


N-{1-[2-(3-chlorophenyl)-2-hydroxyethyl]-3-methyl-2-oxo-3-pyrrolidinyl}-3-chlorobenzamide

Mp. °C: 122-125
MS: [M+H] 407, 409

i) To a stirred suspension of N-{1-[2-(3-chlorophenyl)-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinyl}-3-chlorobenzamide (300mg) in ethanol (4ml) at room temperature was added sodium borohydride (56mg) portionwise. The resulting opaque solution was stirred for 1h then concentrated in vacuo, diluted with water and extracted twice with dichloromethane. The combined extracts was washed with brine, dried over magnesium sulphate, filtered and evaporated to a colourless foam. The title compound was crystallised from diethyl ether as a colourless solid.

Example 123



Diastereoisomer 1: N-{1-[2-(3-chlorophenyl)-2-hydroxyethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide

Mp. °C: 66-68
MS: [M+H] 423, 425

i) N-(3-chlorobenzoyl)-α-(2-oxoethyl)alanine was prepared from methyl α-allylalanine and 3-chlorobenzoyl chloride following the procedures described in example 1 iv to v.

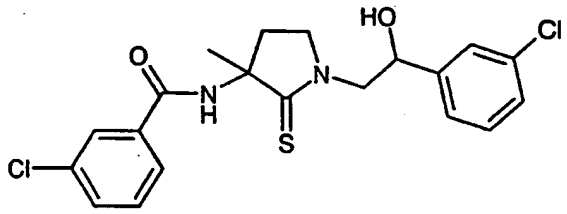
ii) 2-t-Butyldimethylsilyloxy-2-(3-chlorophenyl)ethylamine (3.0g) was added to a stirred solution of N-(3-chlorobenzoyl)-α-(2-oxoethyl)alanine (3.0g) in methanol (45ml) at room temperature under an atmosphere of nitrogen. After 2h the reaction mixture was cooled in an ice bath and sodium borohydride (4.22g) was added portionwise. After 1h at room temperature, the reaction mixture was concentrated in vacuo, diluted with water and extracted twice with dichloromethane. The combined extracts was washed with water and brine, dried over magnesium sulphate, filtered and evaporated to a yellow oil. The oil was heated at reflux in toluene (20ml) under an atmosphere of nitrogen overnight and the solvent removed in vacuo to give N-{1-[2-t-butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-pyrrolidinyl}-3-chlorobenzamide as a yellow oil.

iii) A suspension of N-{1-[2-t-butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-pyrrolidinyl}-3-chlorobenzamide (1.44g) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (0.57g) in toluene (30ml) was heated at reflux under an atmosphere of nitrogen for 40min. The solvent was removed in vacuo and the residue purified on flash silica eluting with dichloromethane-hexane (4:1) and dichloromethane to give N-{1-[2-t-

butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide as a colourless oil.

iv) A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0M, 0.69ml) was added to a stirred solution of N-{1-[2-t-butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide (0.24g) in tetrahydrofuran (8ml). The reaction mixture was stirred at room temperature overnight. After addition of water (1ml), the reaction mixture was evaporated to dryness and the residue purified on flash silica eluting with diethyl ether to give a colourless oil. The resulting mixture of diastereoisomers was separated by preparative HPLC on a 250x20 mm id. KR60-5SIL column eluting at ambient temperature with hexane:tetrahydrofuran:ethanol (70:30:1.5%) at a flow rate of 20ml/min to give diastereomer 1 and diastereomer 2 as colourless solids.

Example 124

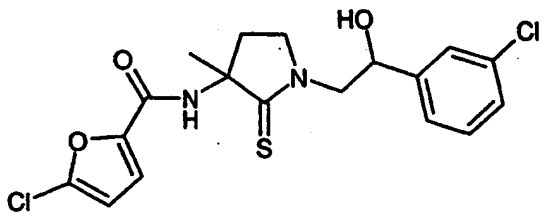


Diastereoisomer 2: N-{1-[2-(3-chlorophenyl)-2-hydroxyethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide

Mp. °C: 126-128
MS: [M+H] 423, 425

i) The title compound was isolated by preparative HPLC from the procedure described in example 123 iv) as a colourless solid.

Example 125



Diastereoisomer 1: 5-Chloro-N-{1-[2-(3-chlorophenyl)-2-hydroxyethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-2-furamide

Mp. °C: 71-73

MS: [M+H] 413, 415

i) 2-t-Butyldimethylsilyloxy-2-(3-chlorophenyl)ethylamine (16.8g) was added to a stirred solution of N-(3-chlorobenzoyl)-α-(2-oxoethyl)alanine (13.7g) in methanol (120ml) at room temperature under an atmosphere of nitrogen. After 3.5h the reaction mixture was cooled in an ice bath and sodium borohydride (0.80g) was added portionwise. After 20min at room temperature, the reaction mixture was concentrated in vacuo, diluted with water and extracted twice with dichloromethane. The combined extracts was washed with water and brine, dried over magnesium sulphate, filtered and evaporated to a yellow oil. The oil was heated at reflux in toluene (120ml) under an atmosphere of nitrogen overnight and the solvent removed in vacuo to give t-butyl 1-[2-t-butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-pyrrolidinylcarbamate as a yellow oil.

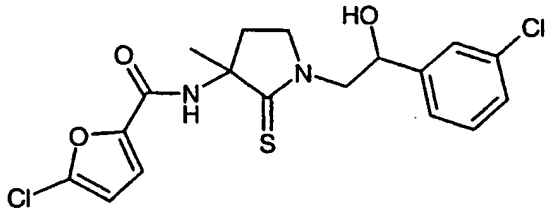
ii) t-Butyl 1-[2-t-butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-thioxo-3-pyrrolidinylcarbamate was prepared following the procedure described in example123 iii) from t-butyl 1-[2-t-butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-oxo-3-pyrrolidinylcarbamate as a colourless oil.

iii) A solution of hydrogen chloride in dioxan (4M, 10ml) was added to a solution of t-butyl 1-[2-t-butyldimethylsilyloxy-2-(3-chlorophenyl)ethyl]-3-methyl-2-thioxo-3-pyrrolidinylcarbamate (1.85g) in dioxan (6ml) and the mixture stirred at room temperature. After 6h, concentrated in vacuo, diluted with water and washed twice

with diethyl ether. The aqueous was made basic with sodium hydroxide (2M) and extracted twice with dichloromethane. The combined extracts was dried over magnesium sulphate, filtered and evaporated to give 3-amino-1-[2-hydroxy-2-(3-chlorophenyl)]ethyl-3-methylpyrrolidin-2-thione as a yellow oil.

iv) Solid 2-chloro-1-methylpyridine iodide (271mg) was added to a stirred solution of 5-chlorofuroic acid (155mg) and triethylamine (210mg) in dried dichloromethane (5ml) at room temperature under an atmosphere of nitrogen. After 1h a solution of 3-amino-1-[2-hydroxy-2-(3-chlorophenyl)]ethyl-3-methylpyrrolidin-2-thione (300mg) in dichloromethane (5ml) was added. After 2h at room temperature, the reaction mixture was washed with aqueous hydrochloric acid (2M), dried over magnesium sulphate, filtered and evaporated to a foam. The crude was purified on flash silica eluting with ethyl acetate-hexane (3:2) to give a colourless foam. The mixture of diastereoisomers was separated by preparative HPLC on a 250 x 20 mm id. KR60-5SIL column eluting at ambient temperature with hexane:tetrahydrofuran:ethanol (80:20:1.5%) at a flow rate of 20ml/min to give diastereoisomer 1 and diastereoisomer 2 as colourless solids.

Example 126



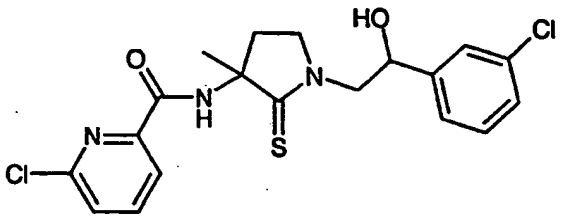
Diastereoisomer 2: 5-Chloro-N-{1-[2-(3-chlorophenyl)-2-hydroxyethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-2-furamide

Mp. °C: 71-73

MS: [M+H] 413, 415

The title compound was isolated by preparative HPLC from the procedure described in example 125 iv) as a colourless solid.

Example 127



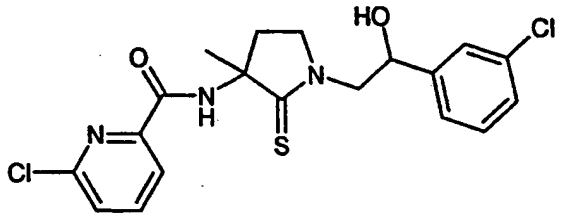
Diastereoisomer 1: 6-Chloro-N-{1-[2-(3-chlorophenyl)-2-hydroxyethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-2-pyridinecarboxamide

Mp. °C: 71-74

MS: [M+H] 424, 426

i) To a stirred solution of 3-amino-1-[2-hydroxy-2-(3-chlorophenyl)]ethyl-3-methylpyrrolidin-2-thione (0.24g) and triethylamine (120mg) in dichloromethane (5ml) was added a solution of 6-chloropyridinecarbonyl chloride (0.17g) in dichloromethane (5ml). After stirring at room temperature for 45min, the reaction mixture was diluted with dichloromethane and washed with aqueous hydrochloric acid (2M), water and brine, dried over magnesium sulphate, filtered and evaporated to colourless foam. The crude was purified on flash silica eluting with ethyl acetate-hexane (3:2) to give a colourless oil. The mixture of diastereoisomers was separated by preparative HPLC on a 250 x 20 mm id. KR60-5SIL column eluting at ambient temperature with hexane:tetrahydrofuran:ethanol (80:20:1.5%) at a flow rate of 20ml/min to give diastereoisomer 1 and diastereoisomer 2 as colourless solids

Example 128



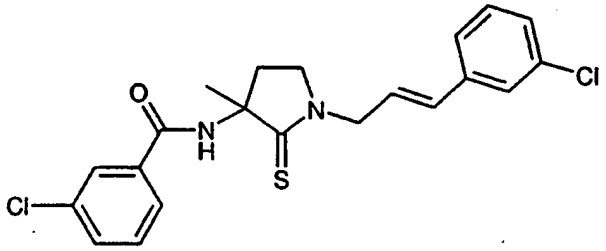
Diastereoisomer 2: 6-Chloro-N-{1-[2-(3-chlorophenyl)-2-hydroxyethyl]-3-methyl-2-thioxo-3-pyrrolidinyl}-2-pyridinecarboxamide

Mp. °C: 72-76

MS: [M+H] 424, 426

The title compound was isolated by preparative HPLC from the procedure described in example 127 i) as a colourless solid.

Example 129



N-{1-[3-(3-chlorophenyl)-2E-propen-1-yl]-3-methyl-2-thioxo-3-pyrrolidinyl}-3-chlorobenzamide

Mp. °C: Glass

MS: [M+H] 419, 421

i) To a stirred solution of 3-(t-butoxycarbonyl)amino-3-methylpyrrolidin-2-one (2.0g) in dried tetrahydrofuran (60ml) at room temperature under an atmosphere of nitrogen was added sodium hydride as a 60% dispersion in oil (0.41g). After 0.5h, a solution of 1-bromo-3-(3-chlorophenyl)-2-propene (2.2g) in dried tetrahydrofuran (15ml) was added dropwise. The reaction mixture was stirred at room temperature for 2h, neutralised with aqueous hydrochloric acid (2M) and diluted with a saturated solution of ammonium chloride. The mixture was extracted with diethyl ether and

the extract dried over magnesium sulphate, filtered and evaporated to an oil. The crude was purified on flash silica eluting with ethyl acetate-hexane (4:1) to give t-butyl 1-[3-(3-chlorophenyl)-2E-propen-1-yl]-3-methyl-2-oxo-3-pyrrodinylcarbamate as a colourless oil.

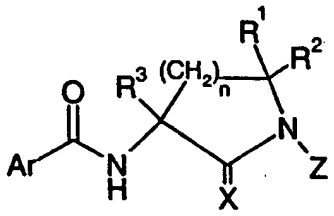
ii) A solution of t-butyl 1-[3-(3-chlorophenyl)-2E-propen-1-yl]-3-methyl-2-oxo-3-pyrrodinylcarbamate (2.18g) in dioxan(12ml) was stirred at room temperature with a solution of hydrochloric acid in dioxan (4M, 10ml) for 3h. The reaction mixture was diluted with aqueous hydrochloric acid (2M) and washed once with diethyl ether. The aqueous was made basic with aqueous sodium hydroxide and extracted twice with dichloromethane. The combined extracts was dried over magnesium sulphate, filtered and evaporated to give 3-amino-1-[3-(3-chlorophenyl)-2E-propen-1-yl]-3-methylpyrrolidin-2-one as an oil.

iii) A solution of 3-chlorobenzyl chloride (0.32g) in dichloromethane (5ml) was added to a stirred solution of 3-amino-1-[3-(3-chlorophenyl)-2E-propen-1-yl]-3-methylpyrrolidin-2-one (0.52g) and triethylamine (0.40g) in dichloromethane (20ml) at room temperature. After 2h the reaction mixture was washed with aqueous hydrochloric acid (2M), twice with water, aqueous saturated sodium bicarbonate, water and brine, dried over magnesium sulphate, filtered and evaporated to a foam. The foam was triturated with diethyl ether to give N-{1-[3-(3-chlorophenyl)-2E-propen-1-yl]-3-methyl-2-oxo-3-pyrrolidinyl}-3-chlorobenzamide as a colourless solid.

iv) A solution of N-{1-[3-(3-chlorophenyl)-2E-propen-1-yl]-3-methyl-2-oxo-3-pyrrolidinyl}-3-chlorobenzamide (200mg) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (106mg) in toluene (5ml) was heated at reflux for 3h. The solvent was removed in vacuo and the residue purified on flash silica eluting with dichloromethane and then dichloromethane-ether (95:5) to give the title compound as a glass.

We Claim:

1. A compound of the formula



wherein,

n is 0, 1 or 2;

X is O, S, NH, or NOH;

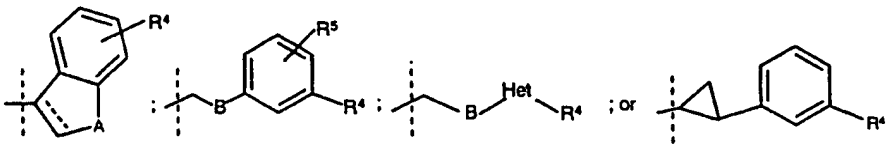
R^1 and R^2 are each independently H, CN, COOR, CONHR, C_1-C_6 alkyl, tetrazole, or R^1 and R^2 together represent "=O";

R is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, -CH_2OH, -CH_2O-alkyl, -COOH;

Ar is an unsubstituted or substituted aromatic or heteroaromatic group;

Z represents a group of the formulae



wherein,

R^4 and R^5 are each independently H, halogen, C_1-C_6 alkoxy , -OAr , C_1-C_6 alkyl, -CF_3, COOR, CONHR, -CN, -OH, COR, -S-(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl)

A is CH_2, O, NR, S, SO, SO_2, CH_2-CH_2, CH_2O, CHOH, C(O); wherein R is as defined above;

B is CHR, CR_2, C_1-C_6 alkyl, C(O), -CHOH, -CH_2-O, -CH=CH, CH_2-C(O), CH_2-S, CH_2-S(O), CH_2-SO_2; -$CHCO_2$R; or –CH-NR_2, wherein R is as defined above

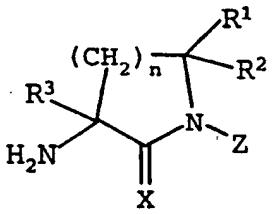
Het is a heterocycle;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1, wherein n is 0 or 1; X is O or S; R^1 and R^2 are each independently H, or R^1 and R^2 together represent "=O"; R^3 is C_1-C_6 alkyl; Ar is meta-substituted aryl (aromatic , heteroaromatic); R^4 is H, F, Cl, or OMe; A is -CH_2-, -O-, or -$(CH_2)_2$-; and B is C_1-C_3 alkyl, methylene, methylmethylene, -CH_2O-, -CH=CH, or -CHOH.

3. A compound as claimed in Claim 2, wherein n is 1; X is S; R^3 is methyl; Ar is 3-bromophenyl, 3-chlorophenyl, 6-chloropyridin-2-yl, or 5-chlorofuran-2-yl; Z is 1-indanyl, 3-chlorophenethyl, or 3-fluorophenethyl; A is –CH_2-; and B is methylene.

4. A compound of formula



wherein n is 0, 1 or 2;

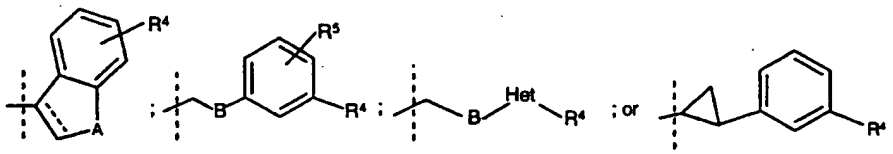
X is O, S, NH, or NOH;

R^1 and R^2 are each independently H, CN, COOR, CONHR, C_1-C_6 alkyl, tetrazole, or R^1 and R^2 together represent "=O";

R is H or C_1-C_6 alkyl;

R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, -CH_2OH, -CH_2O-alkyl, -COOH;

Z represents a group of the formulae



wherein,

R^4 and R^5 are each independently H, halogen, C_1-C_6 alkoxy , -OAr , C_1-C_6 alkyl, -CF_3, COOR, CONHR, -CN, -OH, COR, -S-(C_1-C_6 alkyl), -SO_2(C_1-C_6 alkyl)

A is CH_2; O, NR, S, SO, SO_2, CH_2-CH_2, CH_2O, CHOH, C(O); wherein R is as defined above;

B is CHR, CR_2, C_1-C_6 alkyl, C(O), -CHOH, -CH_2-O, -CH=CH, CH_2-C(O), CH_2-S, CH_2-S(O), CH_2-SO_2; -$CHCO_2R$; or –CH-NR_2, wherein R is as defined above

Het is a heterocycle.

or a pharmaceutically acceptable salt thereof.

5. A composition comprising an effective amount of a compound as claimed in Claim1 in combination with a pharmaceutically acceptable carrier, diluent, or excipient thereof.

6. A composition comprising an effective amount of a compound as claimed in Claim 2 in combination with a pharmaceutically acceptable carrier, diluent, or excipient thereof.

7. A composition comprising an effective amount of a compound as claimed in Claim 3 in combination with a pharmaceutically acceptable carrier, diluent, or excipient thereof.

8. A method of treating a neurodegenerative condition which comprises administering to a patient in need thereof, and effective amount of a compound as claimed in Claim 1.

9. A method of treating pain which comprises administering to a patient in need thereof, and effective amount of a compound as claimed in Claim 1.

10. A compound as claimed in Claim 1 which is rel-(R,R)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-one.

11. A compound as claimed in Claim 1 which is (R,R)-3-[(3-Bromobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-one.

12. A compound as claimed in Claim 1 which is 3-[(3-Chlorobenzoyl)amino]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione.

13. A compound as claimed in Claim 1 which is (S)-3-[(3-Chlorobenzoyl)amino]-1-(3-chlorophenethyl)-3-methylpyrrolidin-2-thione.

14. A compound as claimed in Claim 1 which is (S,R)-3-[(3-Chlorobenzoyl)amino]-1-(1-indanyl)-3-methylpyrrolidin-2-thione.

15. A compound as claimed in Claim 1 which is (S,R)-3-[(6-Chloropyridin-2-yl)carboxamido]-1-(1-indanyl)-3-methylpyrrolidin-2-thione.

16. The use of a compound as claimed in Claim 1, or a pharmaceutically acceptable salt thereof, for antagonizing one or more of the actions of L-glutamate at Group I metabotropic glutamate receptors.

17. The use as claimed in Claim 16 wherein the Group I metabotropic glutamate receptor is mGluR5.

18. The use of a compound as claimed in Claim 1, for the manufacture of a medicament for antagonizing one or more of the actions of L-glutamate at Group I metabotropic glutamate receptors.

19. The use as claimed in Claim 18 wherein the Group I metabotropic glutamate receptor is mGluR5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/08223

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/26 C07D405/12 C07D401/12 C07D405/04 C07D207/24
C07D207/40 C07D211/76 C07D205/085 C07D205/06 A61K31/40
A61K31/445 //(C07D405/12,307:00,207:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MONTOLIU, CARMINA ET AL: "Activation of the metabotropic glutamate receptor mGluR5 prevents glutamate toxicity in primary cultures of cerebellar neurons" retrieved from STN Database accession no. 127:30181 XP002147405 abstract & J. PHARMACOL. EXP. THER. (1997), 281(2), 643-647 , — -/—	1-19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 2000	29/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 00/08223

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOZIKOWSKI, A. P. ET AL: "Synthesis and metabotropic receptor activity of the novel rigidified glutamate analogs (+)- and (-)-trans- azetidine -2,4-dicarboxylic acid and their N-methyl derivatives" retrieved from STN Database accession no. 120:107646 XP002147406 abstract & J. MED. CHEM. (1993), 36(18), 2706-8 ,	1-19
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; FAVARON, MARCO ET AL: "Trans- azetidine -2,4-dicarboxylic acid activates neuronal metabotropic receptors" retrieved from STN Database accession no. 119:217976 XP002147407 abstract & NEUROREPORT (1993), 4(7), 967-70 ,	1-19
A,P	WO 00 26198 A (CLARK BARRY PETER ;HARRIS JOHN RICHARD (GB); LILLY CO ELI (GB); KI) 11 May 2000 (2000-05-11) abstract	1-19